Editorial

Lipofibroadenoma and other rare thymic tumors: a call for misfits

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In this article, den Bakker *et al*. showed a case of lipofibroadenoma of the thymic gland, an extremely rare primary thymic tumor with only thirteen cases reported in the literature (1). This tumor is commonly described as a thymic tumor strongly resembling breast lipofibroadenoma (2). The 2021 World Health Organization (WHO) classification of thymic tumors includes this entity into the group of thymic epithelial tumors (TET), being the only one defined as benign (keep in mind that after the 2015 WHO classification, all thymomas have to be considered as epithelial malignant tumors) (3).

In the reported cases, this tumor is described as a large intrathoracic fatty mass in young patients. This is one of the differences with thymomas, whose peak of incidence is between 50 and 60 years of age (4).

Its origin is uncertain, sometimes being considered as a hamartomatous process and in others being part of a spectrum of thymic adipose tumors such as thymolipoma. The reason for considering lipofibroadenoma as a benign tumor relies on pathologic characteristics, such as absence of atypia, conspicuous proliferative activity, and necrosis (1). Only Aydin *et al*. described signs of invasion of the mediastinal fat (5).

There are no differences in computed tomography (CT) scan or positron emission tomography computed tomography (PET-CT) scan to clearly discriminate this tumor from other thymic tumors (6). This scenario suggests that total thymectomy would be the recommended surgical resection for definitive diagnosis and treatment in these cases, as it is in thymomas (7).

The relationship between thymic lipofibroadenoma, B1 thymoma and autoimmune diseases is noteworthy. Four cases were associated with B1 thymoma and two patients presented with concurrent autoimmune disease, one anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and the other with pure red cell aplasia and B1 thymoma (1). Whether this relationship is significant or not has a simple answer: we do not have enough information. What we know is that the indicated type of resection in B1 thymoma is total thymectomy, which is another argument to perform this technique instead of thymomectomy in lipofibroadenoma.

During the follow-up time of all the published cases (maximum 4 years) no recurrence of the disease or mortality was detected (1). Recurrence and survival are often extrapolated from retrospective studies about the oncologic behaviour of thymoma (5,8,9). Taking into account the peculiar behavior of thymoma, especially concerning its pattern of recurrence, a longer follow-up could be recommended to ensure that thymic lipofibroadenoma is a benign tumor.

A light in the dark has been kindly offered by den Bakker *et al*. with their molecular analysis, hoping to contribute to the integrated genomic landscape of TET, pioneered by Radovich *et al*. (10). No relevant somatic mutations or genetic rearrangements were identified. This is important because we know that the HMGA-2 mutation described in thymolipoma and GTF2I mutation linked to thymomas A and AB are not present in lipofibroadenoma (1,10). However, we need more information to confirm this

genomic pattern.

The constitution of the International Thymic Malignancy Interest Group (ITMIG) in 2010, led by Frank Detterbeck, was a fundamental initiative to build a worldwide multidisciplinary community willing to participate in a global database that has been crucial for obtaining evidence-based information about thymic malignancies, even refining WHO histological classification (11,12).

The ITMIG study published in 2014 by Huang *et al.* relied on a large international database filled with retrospective data of 47 institutions spanning 15 countries, with a total of 6,097 cases recorded over a 6-month period. In this case, only patients with thymoma, thymic carcinoma, or thymic carcinoid were included (13). Another surprising publication was the Réseau tumeurs THYMIques et Cancer (RYTHMIC) prospective cohort. Beyond its objectives and results, the fact is that the national network of thymic epithelial malignancies in France was able to register a total of 2,600 patients with TET in a period of 6 years (14). Any of these studies included rare thymic tumors such as lipofibroadenoma.

These initiatives suggest that thymic tumors are a rare disease, and some histologic types are commonly underreported. Additionally, these entities are often excluded from studies in order to obtain more consistent results. More information is needed in order to better determine the epidemiology, clinic, treatment and prognosis. The little evidence we have on lipofibroadenoma and other rare thymic tumors suggest that the entire scientific community has to make an effort to report these cases to improve our knowledge about them, because it seems that these "misfits" have something to say.

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A quest for evidence supporting operative intervention for cystic lesions in the mediastinum

Incidental finding of cystic lesions in the mediastinum usually prompts consultation to thoracic surgeons. During my training I learned that except for asymptomatic small pericardial cysts, all other mediastinal cysts should be surgically excised (1). However, this recommendation appears to be based on opinions instead of controlled scientifically sound studies.

The goal of this series was to systematically review the available literature and provide a comprehensive document about mediastinal cysts that includes etiology, clinical presentation, radiologic characteristics, treatment modalities, surgical indications, incidence of complications and recurrence.

The most common presentation of a mediastinal cyst is as incidental finding on a chest computed tomography (CT) scan (2). As such, our series starts with a comprehensive review of radiological characteristics of different types of mediastinal cystic lesions. We then review the literature supporting indications for surgical excision based on anatomic location, presence of symptoms and potential for malignancy. We later describe different surgical approaches and include an editorial about the incidence of complications and recurrence. Finally, the authors focus on the most common mediastinal cysts: bronchogenic, esophageal duplication, thymic and pericardial cysts.

The purpose of this work is to serve as a quick reference for health care providers (specifically thoracic surgeons) to make educated decisions about the management of mediastinal cysts.

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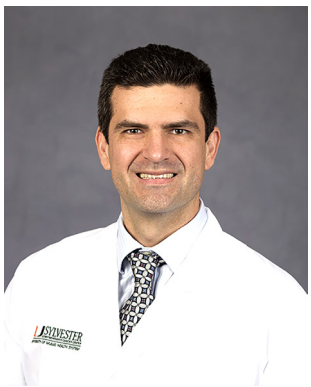

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Original Article

Intralesional microbleeding in resected thymic cysts indeterminate on imaging

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Background: The propensity of thymic cysts to mimic solid thymic epithelial tumors (TETs) on computed tomography (CT), on account of attenuation values greater than water and thickened or calcified walls, can lead to non-therapeutic thymectomy. These lesions can fluctuate in volume, CT attenuation, and magnetic resonance imaging (MRI) signal over time. We hypothesized that spontaneous hemorrhage and resorption may contribute to their variable appearance over time.

Methods: Completely excised thymic cysts were identified retrospectively over a 20-year period by their pathologic diagnosis. Cysts were excluded if they did not have available presurgical imaging, were not prevascular, were located within or contained an enhancing mass by imaging, or were of non-thymic origin upon microscopic review. Histopathological analysis of all available resected thymic cyst material and radiologic analysis of the cysts on pre-operative imaging were performed.

Results: Upon application of exclusion criteria, we identified 18 thymic cysts from the initial 85 mediastinal cystic specimens. Most cysts were unilocular (11/15, 73%), showed turbid-to-semisolid, hemorrhagic fluid (10/12, 83%) and showed histopathological findings suggestive of intralesional microbleeding (14/18, 78%), remodeling (8/18, 44%), pathological wound healing/scarring of the capsule (16/18, 89%), and fat necrosis in the surrounding thymic tissue (12/18, 67%). On CT, 6/17 (35%) cysts demonstrated wall calcification. Sixty-five percent (11/17) had attenuation values ≥20 Hounsfield units (HU). Two of the 4 cysts imaged by MRI were T1-isointense, one was mixed hyper- and isointense, and one T1-hypointense to muscle, with iso- and hyperintensity indicating hemorrhagic or proteinaceous content. Twenty-five percent (1/4) of cyst walls imaged by MRI were T1/T2-hypointense, indicating presence of calcification, hemosiderin, and/or fibrosis.

Conclusions: Resected thymic cysts in this cohort often showed features suggestive of intralesional microbleeding, inflammation, and fibrosis, which may explain their appearance and behavior over time on CT and MRI.

Keywords: Thymic cyst; hemorrhage; thymoma; CT interpretation pitfalls; non-therapeutic thymectomy

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Introduction

Thymic cysts are benign lesions that can be misinterpreted on computed tomography (CT) as thymic epithelial tumors (TETs) by experienced radiologists and thoracic surgeons, leading to non-therapeutic thymectomy (1).

Several studies have reported non-therapeutic thymectomy rates greater than 25% (1-3). A more recent investigation showed that a majority of unilocular thymic cysts, as defined by an index magnetic resonance imaging (MRI) examination and followed for more than 5 years, changed in volume (91%), CT attenuation (43%), and T1-weighted MRI signal intensity (67%) over time. Additionally, 16% of unique thymic cysts developed wall calcification at some point during this longitudinal study, and a majority also had CT attenuation values greater than that of water, indicating hemorrhagic and/or proteinaceous content. The thymic cysts ranged in attenuation from 0 to 100 Hounsfield units (HU). These described imaging features on CT mimic those of solid, malignant thymic neoplasms, which may explain their misinterpretation. No thin-walled unilocular thymic cyst, as initially defined by MRI, developed irregular wall thickening, mural nodularity, or septations during more than 5 years of follow-up (4). Malignant transformation of thymic cysts has been reported as extremely rare and to occur almost exclusively in multilocular thymic cystic lesions (5-10). However, review of these case reports of "transformed" multilocular thymic cysts brings to light that the occurrence of malignant transformation has been presumed, exclusively on the basis of the finding of cancer in the cyst wall. No case report that we have found provides prior imaging or other information to prove that the lesion commenced as a benign thymic cyst and subsequently transformed. In a case report describing a unilocular cystic thymic lesion that "transformed into" a papillary adenocarcinoma (5), the imaging at presentation showed the lesion to have an irregular, lobulated, asymmetrically-thickened wall on CT, features more compatible with a cystic thymoma or cystic thymic carcinoma, than a benign thymic cyst (6-9). Hence, to date and to our knowledge, there may be no proof of malignant transformation of these lesions in the literature.

We performed this study to examine the histopathological basis for the fluctuation in size and appearance of these lesions over time, which continues to baffle CT interpretation and affect surgical decision-making. We hypothesized that chronic, recurrent hemorrhage and resorption may explain the fluctuation in size, CT attenuation, and T1-weighted MRI signal of these lesions. We present the following article in accordance with the STROBE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-22-42/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This Health Insurance Portability and Accountability Act (HIPAA)-compliant study was reviewed and approved by the Mass General Brigham (MGB) Institutional Review Board (IRB), under the protocol number 2020P000187, and informed individual consent for this retrospective analysis was waived.

Case identification

The Massachusetts General Hospital (MGH) Pathology Archives Database search for the terms "*thymic cyst*", "*mediastinal cyst*", and "*thymic bed cyst*" was performed to identify completely excised mediastinal cysts between April 2000 and May 2020. The resultant cases were reviewed, and final diagnoses were made based on histological and/or immunohistochemical (IHC) studies by a board-certified pathologist. The diagnostic hematoxylin and eosin (H&E)-stained slides, along with ancillary immunohistochemical stains, if present, were retrieved from MGH surgical pathology archives. The diagnostic criteria were based on prior published classifications of mediastinal cystic lesions (11).

Inclusion criteria for this study were: (I) a confirmed pathological diagnosis of benign thymic cyst after a microscopic assessment of the diagnostic histological material; (II) completely resected, rather than partially sampled lesions; (III) available preoperative cross-sectional imaging; and (IV) available histopathological material. Upon imaging review, cases were excluded if the epicenter of the lesion was not in the upper two-thirds of the prevascular mediastinum or if the cyst was located within,

or contained, an enhancing mass.

Demographic data and clinical course

Demographic and clinical data were obtained from the MGH electronic medical record. Demographic and clinical data included age at surgery, sex, race, anatomic site, tumor size, body mass index (BMI, in kg/m^2), presenting symptoms, comorbidities, clinical indication for imaging studies, and clinical indication for surgical resection.

Histopathological evaluation

Gross pathological data on the resections and hematoxylin and eosin (H&E)-stained slides included: specimen measurements, cyst dimensions (including gross maximum diameter), architectural macroscopic configuration (unilocular or multilocular), cyst fluid characteristics (when available), and nature of the excision (intact *vs.* disrupted or morcellated).

Prior to the microscopic evaluation of the retrieved diagnostic H&E-stained slides, a joint panel of two pathologists and a subspecialty-trained thoracic radiologist with 24 years of experience defined and selected by full consensus the histopathological features to be systematically collected in each case.

Re-analysis of the histopathological features of the cyst epithelial lining, cyst wall, surrounding thymus, and cavity contents was performed for this study by a board-certified pathologist who was blinded to clinical and radiological data. A detailed list of the microscopic findings evaluated in this study is provided in the Supplementary file (Table S1).

Imaging analysis

The CT and/or MRI performed closest to the date of surgery for each patient was reviewed on a Visage (Version 7.1.15, Build 3056) Picture Archive and Communication System (PACS) by a subspecialty-trained thoracic radiologist with 24 years of experience. The following data (Table S2) for each cyst were recorded: size—transverse, anteroposterior, and craniocaudal; morphology—round, oval, saccular, lobulated-saccular; locularity—unilocular, multilocular, indeterminate; qualitative CT attenuation relative to non-fatty chest wall musculature on the same image; quantitative CT attenuation in HU by round or elliptical (depending upon cyst shape) region-of-interest (ROI) placement over as much of the fluid component of the lesion as possible and excluding artifacts to the greatest degree possible; T1-weighted and T2-weighted MRI signal relative to muscle—hyper-, iso-, or hypointense; character of cyst wall on CT, whether thin and smooth, irregular, nodular, or a mixture of these; presence of wall enhancement on MRI (not evaluable by CT as only one CT was performed without and with intravenous (IV) contrast and wall of this cyst on CT was not discernible); maximal wall thickness on contrast-enhanced CT; maximal wall thickness on post-contrast MRI; presence of calcification; distribution of calcification—punctate or circumferential; and T1- and T2-weighted wall signal on MRI. A box listing the CT and MRI scanner hardware and software is provided in the Supplementary file (Box S1).

Statistical analysis

Descriptive summary statistics were summarized for the overall cohort. The data was analyzed using Microsoft Excel, and the results reported as mean ± one standard deviation (SD). Missing data was reported when applicable.

Results

We found a total of 85 completely resected mediastinal cyst specimens from 85 patients in the MGH Pathology Archives Database over the 20-year study period. Of these, 33 lesions were classified as thymic cysts. Upon review of the exclusion criteria, we identified 18 thymic cysts that met our pre-specified criteria. A flow diagram of the study cohort is provided in *Figure 1*. The nature of the remaining mediastinal cysts is provided in Table S3 of the Supplementary file.

Clinical characteristics

Patient demographics are provided in *Table 1*. The median age at resection was 60.5 (range, 45–77 years). The female:male ratio was 1.3. Most cysts were found incidentally (10/18, 56%) in the setting of CT imaging performed for other reasons (e.g., low-dose CT screening of smokers). Based upon preoperative imaging, only 3 cysts were classic simple cysts but were nonetheless removed (1 was incidental to concomitant coronary bypass surgery, 1 was clinically suspected to be a brachial cleft cyst, and 1 was removed due to patient preference). The other 15 patients had imaging features interpreted as most consistent with a complex cystic lesion or a thymic tumor.

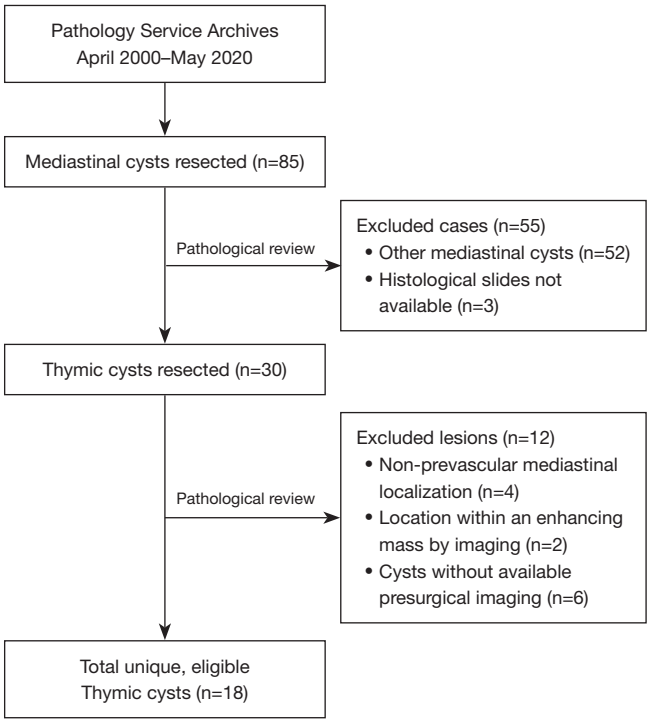

Figure 1 Flowchart shows the inclusions and exclusions that yielded the final study cohort of pathologically and radiologically eligible thymic cysts cases for the full study cohort.

Cysts were often found in asymptomatic patients (8/18, 44%), but also in patients presenting with chest pain (5/18, 28%), shortness of breath (2/18, 11%), or cough (2/18, 11%).

Gross pathological findings

All cysts were completely excised, but three were disrupted on macroscopic examination and, in all of these, the intracystic fluid was discarded at the time of surgery and pathologic examination and therefore unavailable for direct examination for the purpose of this study. Most cysts were unilocular (11/15, 73%), with a gross maximum diameter range of 1.5–11.2 cm (mean ± SD: 4.2±2.7 cm). When reported prior to fluid discard at time of surgery or at initial histopathologic evaluation, most cysts contained turbid-to-semi-solid, tan, hemorrhagic fluid (10/12, 83%); only two cysts (2/12, 17%) contained clear, serous-appearing fluid.

Histopathological microscopic characteristics

Diagnostic H&E-stained slides were analyzed histopathologically. Detailed histopathologic findings of the retrieved thymic cysts are described in *Table 2*.

Table 1 Patient demographics

Characteristics	Number of cases [%]
Age (years), mean ± SD	60.5±9.9
Sex ratio (F:M)	1.3
BMI (kg/m^2), mean ± SD	27.9±4.0
Symptoms	
Asymptomatic	8 [44]
Chest pain	5 [28]
Shortness of breath	2 [11]
Cough	2 [11]
Other	2 [11]
Concomitant conditions	
None	12 [67]
History of thromboembolic events	3 [17]
History of smoking	3 [17]
Connective tissue disease	4 [22]
NSIP	1 [6]
Hashimoto's thyroiditis	2 [11]
Mixed connective tissue disease	1 [6]
Dermatomyositis	1 [6]
Primary biliary cirrhosis	1 [6]
Sjögren's	1 [6]
Neoplastic	0
Other	4 [22]

SD, standard deviation; M, male; F, female; BMI, body mass index; NSIP, nonspecific interstitial pneumonia.

Findings suggestive of recent microbleeding and trauma or inflammation

Most thymic cysts (14/18, 78%) showed findings suggestive of intralesional microbleeding, trauma, and/or inflammation in the capsule or cavity of the cyst (*Figures 2,3*), which included: stromal capsular hemorrhage (10/18, 55%), fibrin deposition in the lumen wall (4/18, 22%), patchy epithelial denudation (6/18, 33%), hemosiderin deposition in the capsule (8/18, 44%) or in the cavity contents (7/18, 39%), and presence of hemosiderin-laden macrophages in the

Table 2 Histopathological features of thymic cysts

Microscopic findings	Number of cases [%]
Findings suggestive of microbleeding and trauma	14 [78]
Stromal capsular hemorrhage	10 [55]
Luminal fibrin deposition	4 [22]
Focal epithelial denudation	6 [33]
Extracellular hemosiderin deposition	
In capsule	8 [44]
Inside cyst cavity	7 [39]
Hemosiderin-laden macrophages	6 [33]
Findings suggestive of remodeling and organization	8 [44]
Granulation tissue	5 [28]
Histiocyte lining in areas of denudation	2 [11]
Cholesterol clefts in capsule or cavity	3 [17]
Foam and/or giant cells	3 [17]
Acute Inflammatory infiltrate	2 [11]
Findings suggestive of chronicity and scarring	16 [89]
Chronic inflammatory infiltrate	12 [67]
Capsular fibrosis	12 [67]
Hyalinosis	11 [61]
Calcifications	6 [33]
Heterotopic osseous and myeloid metaplasia	1 [6]
Findings in adjacent thymic tissue	18 [100]
Involution	16 [89]
Fat necrosis	11 [61]
Microcystic Hassall's corpuscle formation	5 [28]
Lymphoid follicular hyperplasia	3 [17]
True thymic hyperplasia	1 [6]

cyst cavity (6/18, 33%). Additionally, most cases showed fat necrosis in the surrounding thymic tissue (12/18, 67%). Patchy necrosis and necrotic debris were also commonly seen in the capsule (7/18, 39%) and cavity (8/18, 44%), respectively.

Findings suggestive of remodeling and organization

A large proportion (8/18, 44%) of thymic cysts also showed findings suggestive of recent remodeling or reorganization of their architecture (*Figures 4,5*), which included: presence of granulation tissue (5/18, 28%) and histiocytic lining (2/18, 11%) in areas of epithelial denudation, presence of cholesterol clefts in the capsule or cavity (3/18, 17%), presence of acute inflammatory infiltrate (2/18, 11%), and presence of foam and/or giant cells in the capsule (3/18, 17%).

Findings suggestive of chronicity and established fibrosis

An overwhelming majority of cysts (16/18, 89%) showed findings suggestive of chronicity, pathological wound healing, and scarring of the capsule, including: presence of chronic inflammatory infiltrate (12/18, 67%), collagenous fibrosis (12/18, 67%), hyalinosis (11/18, 61%), calcifications (6/18, 33%), germinal center formation (3/18, 17%), and heterotopic osseous and myeloid metaplasia (1/18, 6%).

Additional findings in the surrounding thymus

The surrounding thymic tissue was involuted in most resections (14/18, 78%). Lymphoid thymic hyperplasia was present in three cases, and true thymic hyperplasia was seen in one case. Microcystic Hassall's corpuscle formation was seen in a number of cases (5/18, 28%).

Imaging findings

A total of 17/18 (94%) thymic cysts were imaged preoperatively by CT, with 3/18 by both CT and MRI and 1/18 (6%) exclusively by MRI. 12/17 (70%) CTs were performed with iodinated IV contrast, 4/17 (24%) CTs were performed without IV contrast, and 1/17 (6%) was performed without and with IV contrast. All 4 (4/4) MRIs were performed without and with IV contrast (gadolinium). The mean ± SD, median, and range of the interval between preoperative imaging and surgery in days was for CT (n=17): 69±57, 49, 6–224 days and for MRI (n=4): 55±57, 53, 11–103 days.

On CT, 11/17 (65%) thymic cysts had attenuation values ≥20 HU indicative of hemorrhagic and/or proteinaceous content. A total of 6/17 (35%) cysts demonstrated wall calcification. Fifty percent (2/4) of cysts imaged by MRI were T1-isointense, 1/4 (25%) was mixed T1-hyper- and isointense, and 1/4 (25%) T1-hypointense to muscle, with latter two T1-weighted signal characteristics compatible with hemorrhagic and/or proteinaceous content. One of the four (25%) cyst walls imaged by MRI was T1/

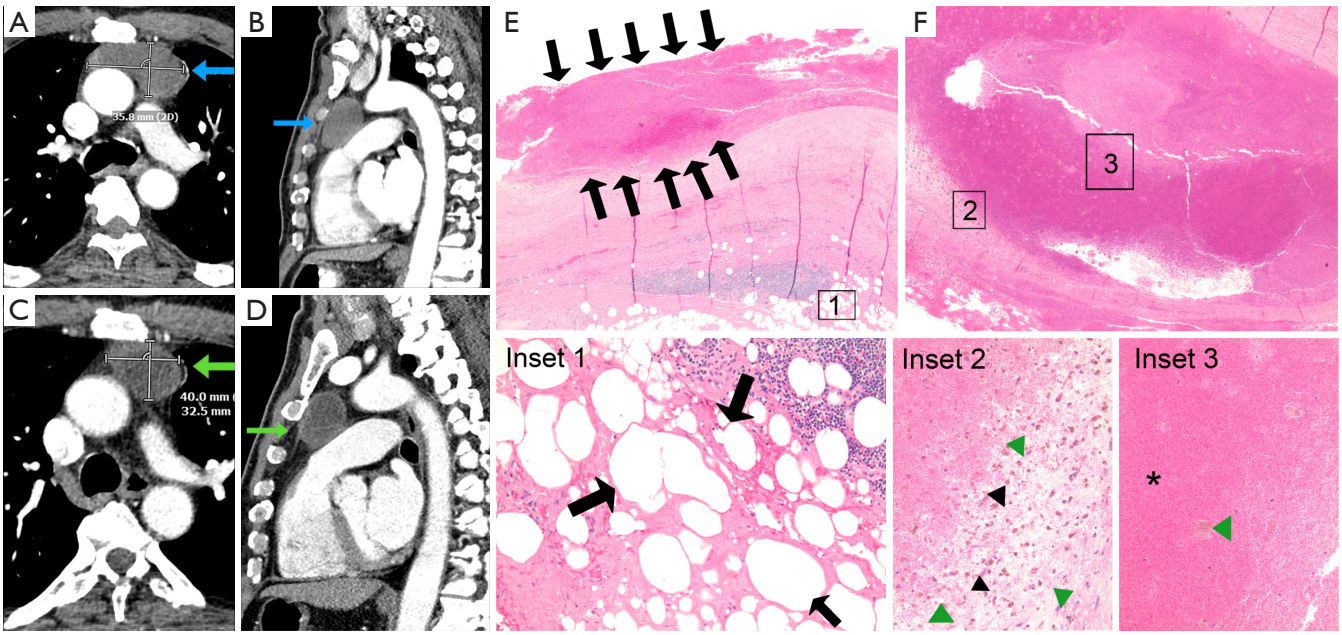

Figure 2 Axial and sagittal chest CT with IV contrast of a 63-year-old man (A,B) performed 8 months prior to surgery show a 65 mm × 36 mm × 48 mm (TRV, AP, CC), 39 HU cystic lesion (blue arrows), with this attenuation value indicating hemorrhagic and/or proteinaceous content. Pre-operative axial and sagittal IV contrast-enhanced images (C,D) show a smaller, 40 mm × 32 mm × 43 mm (TRV, AP, CC) cyst, of lower attenuation (15 HU), and with an irregularly thickened wall (green arrows). Histologic images of H&E-stained sections of the completely resected thymic cyst show the fibrotic cyst wall of the cyst (E, ×40 magnification on microphotograph) with fibrin thrombus attached to the luminal side of the wall (black arrows). The surrounding involuted thymic tissue (inset 1, ×200 magnification on microphotograph panel E) shows fat necrosis (black arrows). There is large fresh capsular hemorrhage contained within the fibrotic wall (F, ×100 magnification on microphotograph). The capsular hemorrhage (insets 2 and 3, ×200 magnification on microphotograph panel F) shows granulation tissue with myofibroblast proliferation (black arrowheads), hemosiderin deposition (green arrowheads), and fresh red blood cells (asterisk). CT, computed tomography; IV, intravenous; TRV, transverse; AP, anteroposterior; CC, craniocaudal; HU, Hounsfield units; H&E, hematoxylin and eosin.

T2-hypointense, indicating presence of calcification, hemosiderin, and/or fibrosis in the wall. The accompanying CT showed wall calcification. Two of the four cysts imaged by MRI were multilocular, one of the four was unilocular, with an irregularly thickened, enhancing wall, and the fourth cyst imaged by MRI was unilocular with thin, smooth wall enhancement, though misinterpreted as solid on account of an interpretive pitfall related to a suboptimal MRI protocol in 2004. A complete tabulation of recorded CT and MRI characteristics of the thymic cysts is provided in Table S4.

Discussion

In this case series of resected thymic cysts, we report a high proportion of histopathological findings suggestive of microbleeding, remodeling, and wound healing in these lesions. The fairly common finding of adjacent fat necrosis suggests prior trauma, infection, or inflammation as an inciting agent. The T1/T2-weighted MRI signal characteristics and the CT attenuation of the majority of resected cysts were consistent with hemorrhagic and/or proteinaceous content. The irregularity and thickening of some of the walls on CT and MRI, in the setting of benign disease, therefore may have represented sequelae of chronic recurrent hemorrhage and/or inflammation. As shown in prior studies, thymic cysts can mimic thymic neoplasms on imaging (1), on account of their fluctuation in volume, CT attenuation, and MRI signal over time and on account of wall thicknesses exceeding 3 mm (4). However, the cause of these changes has not been investigated until now.

As most of our cases showed evidence of recent

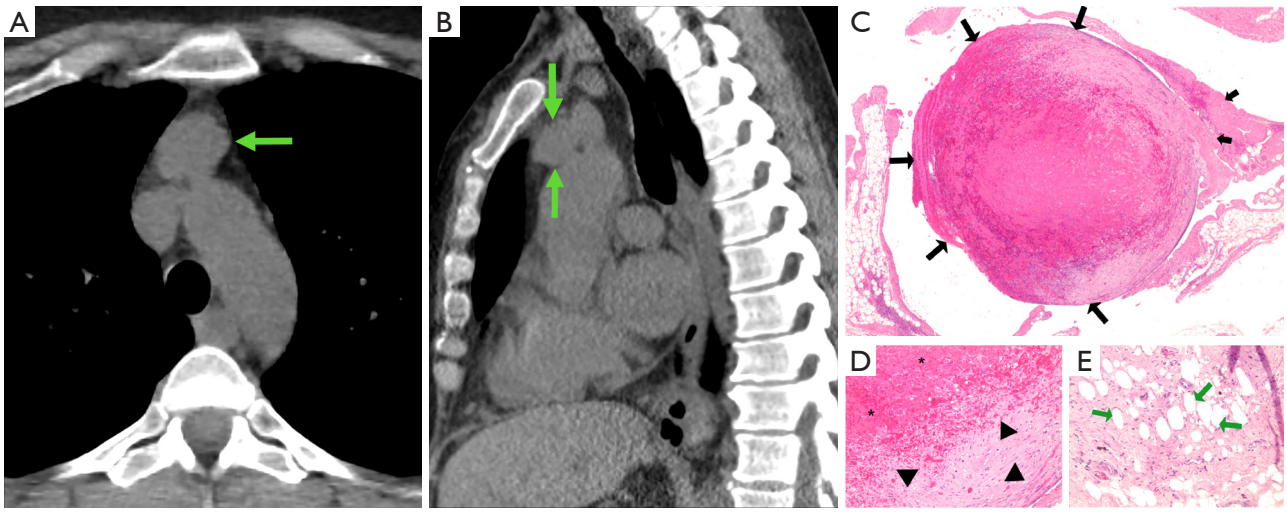

Figure 3 Axial and sagittal non-contrast chest CT images of a 46-year-old woman (A,B) show a 26 mm × 24 mm × 29 mm (TRV, AP, CC), lobulated, well-circumscribed, 27 HU, homogenously attenuated mass in the thymic midline (green arrows), differential diagnosis of which includes an isoattenuating hemorrhagic and/or proteinaceous thymic cyst, whether unilocular or multilocular, and a TET, with isolated prevascular lymphadenopathy less likely. Histologic images of H&E-stained sections of the completely resected thymic cyst show a large organizing thrombus (C, ×40 magnification on microphotograph, long black arrows) attached to the cyst wall on the luminal aspect of the cyst (short black arrows). The thrombus (D, ×200 magnification on microphotograph) shows organizing granulation tissue with myofibroblast proliferation (black arrowheads), surrounding the fibrin clot (asterisks). The surrounding involuted thymic tissue (E, ×200 magnification on microphotograph) shows degenerating adipocytes that have lost their nuclei (green arrows) and are surrounded by fibrosis and chronic inflammation, consistent with fat necrosis. CT, computed tomography; TRV, transverse; AP, anteroposterior; CC, craniocaudal; HU, Hounsfield units; TET, thymic epithelial tumor; H&E, hematoxylin and eosin.

microbleeding along the luminal surface of the cyst, increases in volume of the total cyst fluid due to blood spillage into the cyst cavity could hypothetically increase the intraluminal pressure, further increasing the wall tension of the cyst and precipitating more bleeding and remodeling. Spontaneous bleeding within the thymus has been reported in a previously healthy patient with sudden-onset left-side chest pain, in which a thymic cystic mass progressively enlarged 18 days after initial imaging at presentation, prompting surgical resection, The resected specimen demonstrated an enlarged hemorrhagic thymus with a hemorrhagic cavity. Microscopic examination revealed a normal involuted thymus with scattered thymic tissue and significant hemorrhage in the medulla (12). As several studies have demonstrated that mechanical tension drives tissue remodeling through different mechanisms, including fibroblast-to-myofibroblast transition (13,14), we hypothesize that continuous stress to the wall of thymic cysts with intralesional bleeding could lead to tissue remodeling, fibrosis, and subsequent resorption. As expected, we found histological evidence of tissue remodeling (8/18, 44%) and/or pathological wound healing (16/18, 89%) in an overwhelming majority of cysts, which may explain the fluctuation in size, CT attenuation, and MRI signal of these lesions over time and which correlated with the presence of wall calcification on CT in some of the cysts in this study and others (4). Similar fluctuations in benign cyst size have also been reported in other organs such as the adrenal glands, in which resorption has also been reported (15).

The cause of initial bleeding in the lesions is unknown. It may be due to both external (mechanical forces) and internal (architectural abnormalities) causes. Interestingly, most of our cases (67%) showed fat necrosis in the surrounding thymic tissue, which has been associated with mechanical trauma, infection, and inflammation in other tissue types of the body (16,17).

Based on these findings and those of preceding literature (1,4,18), we propose an updated clinical management algorithm for the finding of an indeterminate round or

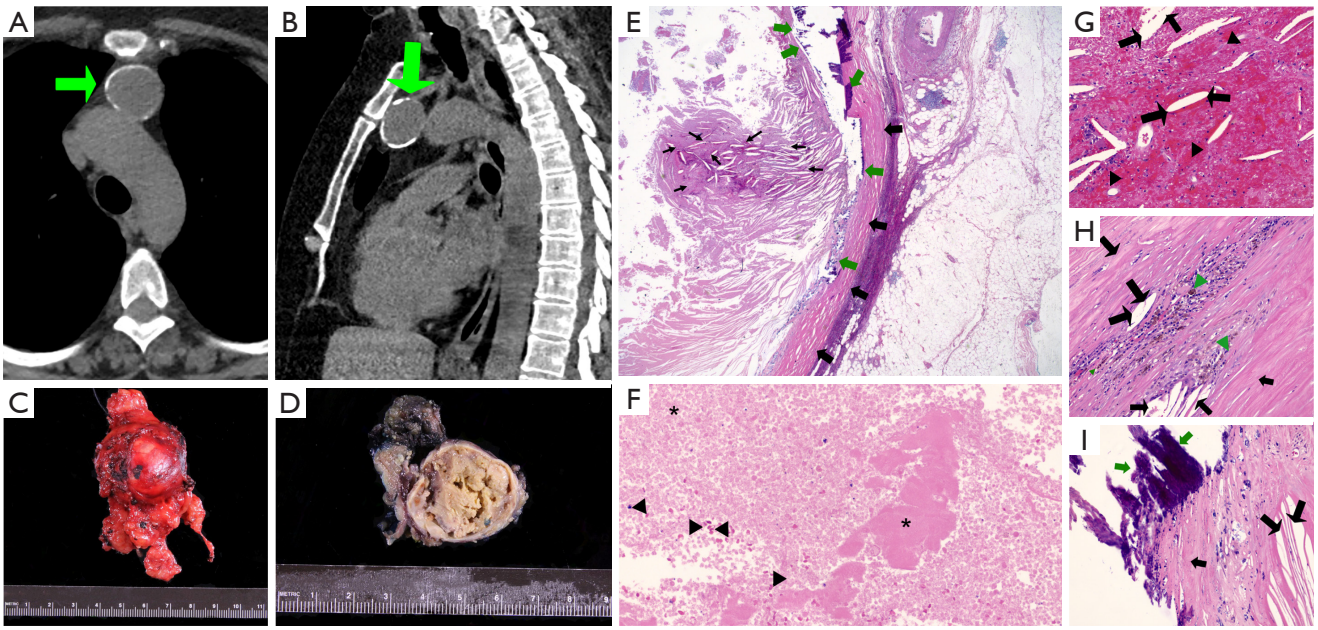

Figure 4 Axial and sagittal non-contrast chest CT images of a 62-year-old woman (A,B) show a 31 mm × 31 mm × 37 mm (TRV, AP, CC), 25 HU isoattenuating lesion, with wall calcification (green arrows). Differential diagnosis includes a rim-calcified, hemorrhagic and/or proteinaceous thymic cyst, a dermoid cyst, and a cystic thymoma. Resected specimen shows a round cystic lesion with attached remnant of thymus (C), and internal semi-solid tan contents on sectioning (D). Histologic images of H&E-stained sections of the thymic cyst resection showing capsule (E, ×40 magnification on microphotograph) with collagen fibrosis (black thick arrows), with multifocal calcifications (green thick arrows), and prominent cholesterol cleft formation in the luminal aspect (black thin arrows). On high magnification, the cystic cavity (F and G, ×200 magnification on microphotographs) contains proteinaceous debris (asterisks), fresh red blood cells (black arrowheads), and cholesterol clefts (black arrows). On high magnification, the capsule (H and I, ×200 magnification on microphotographs) has collagen fibrosis (short black arrows), cholesterol clefts (long black arrows), hemosiderin deposition (green arrowheads), and calcifications (green arrows). CT, computed tomography; TRV, transverse; AP, anteroposterior; CC, craniocaudal; HU, Hounsfield units; H&E, hematoxylin and eosin.

saccular, well-circumscribed, homogeneous attenuation thymic nodule or mass measuring less than or equal to 100 HU on CT (*Figure 6*).

Our study has several limitations. First, it is retrospective. Second, there is selection bias which likely yielded a greater proportion of cysts with hemorrhagic findings than reflect true prevalence—only resected lesions were examined. Third, preoperative imaging was not performed on the same day as the surgery, hence more precise correlation between imaging findings and histopathology could not be made. Fourth, the presence of the histological findings of microbleeding in this study may not necessarily imply causality.

Conclusions

We report that a large proportion of completely resected thymic cysts exhibited histopathological evidence of microbleeding, remodeling, and wound healing; findings which correlated with preoperative imaging. Clinicians and pathologists involved in the diagnosis of these lesions should be aware that the variable imaging characteristics and behavior of thymic cysts over time may be secondary to intralesional bleeding and resorption and that these features, in the absence of other concerning imaging features, can be benign. If clinical concern remains regarding the imaging findings of a probably benign, but indeterminate cystic thymic lesion, MRI surveillance could be undertaken to

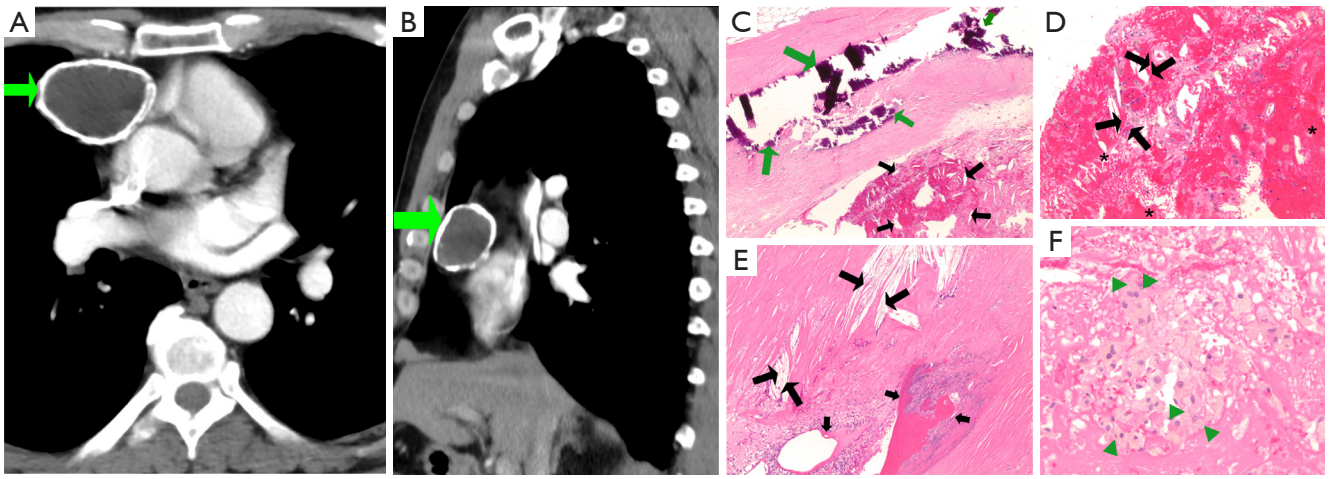

Figure 5 Axial and sagittal intravenous contrast-enhanced chest CT (A,B) images of a 56-year-old man shows a 56 mm × 41 mm × 46 mm (TRV, AP, CC), water attenuation, unilocular cyst with a calcified wall measuring up to 5 mm in thickness in the right prevascular mediastinum (green arrows), compatible with a thymic cyst, although a dermoid cyst and cystic thymoma remain considerations. Histologic images of H&E-stained sections of the completely resected thymic cyst show a fibrotic capsule (C, ×40 magnification on microphotograph) with calcifications (green arrows) and abundant cholesterol cleft formation in the cavity (thin black arrows). On higher magnification (D, ×100 magnification on microphotograph), the cavity contains abundant cholesterol clefts (black arrows), and fresh hemorrhage (asterisks). The fibrotic capsule (E, ×100 magnification on microphotograph) also has cholesterol clefts (black long arrows) and additionally shows osseous metaplasia and bone marrow formation (black short arrows). The cavity (F, ×400 magnification on microphotograph) contains abundant hemosiderin-laden macrophages with frothy-pigmented cytoplasm (green arrowheads). CT, computed tomography; TRV, transverse; AP, anteroposterior; CC, craniocaudal; H&E, hematoxylin and eosin.

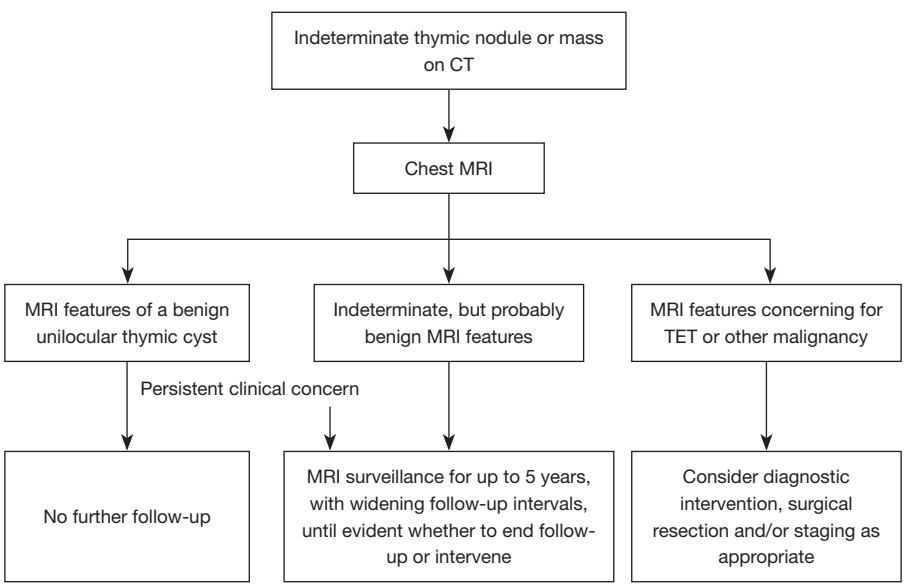

Figure 6 Proposed clinical management algorithm for an indeterminate thymic nodule or mass on imaging. CT, computed tomography; MRI, magnetic resonance imaging; TET, thymic epithelial tumor.

confirm benign behavior over time, with the aim to reduce the rate of non-therapeutic thymectomy.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Mass General Brigham Institutional Review Board, under the protocol number 2020P000187, and individual consent for this retrospective analysis was waived.

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Review Article

Anatomy of mediastinal veins and nerves

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Abstract: The mediastinum is the central compartment in the thoracic cavity that lies between the lungs. It extends from the thoracic inlet superiorly to the diaphragm inferiorly and sternum anteriorly to the vertebral column posteriorly. It is commonly divided into four compartments—superior, anterior, middle and posterior mediastinum. However, some have started to classify it into the more recent three compartments—anterior (prevascular), middle (visceral) and posterior (paravertebral). The mediastinum is of clinical significance because many vital structures, such as the heart, great vessels, esophagus, lymphatics, and trachea, lie within these compartments. Disease presentation can greatly vary depending on the structures involved, and the differential diagnosis can range widely. Therefore, knowledge of the anatomy and subdivisions of the mediastinum is vital for thoracic surgeons. Herein, we have provided a brief review of the mediastinal anatomy. Utilizing the four-compartment model, we detail the contents of each compartment of the mediastinum with special attention to its veins and nerves. There are also several venous junctions that are important for mediastinal surgery, such as the internal jugular-subclavian venous junction and the left-right brachiocephalic venous junction. We describe useful superficial landmarks, such as the sternocleidomastoid and manubrium, and how they relate to some of the key venous junctions.

Keywords: Mediastinal surgery; video assisted thoracic surgery (VATS); azygous vein; superior vena cava (SVC); inferior vena cava (IVC)

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Introduction

The mediastinum is frequently encountered by thoracic surgeons for both benign and malignant disease. As part of a special series on the mediastinum, this article is meant to serve as a brief review of mediastinal anatomy and supplement the other articles within the series. This manuscript focuses on the surgical anatomy of the mediastinal veins and nerves and reviews surface landmarks for vein connections. The mediastinum is generally understood as four anatomical compartments.

Superior mediastinum

The borders of the superior mediastinum include the thoracic aperture superiorly, the angle of Louis anteriorly, and the T4/T5 vertebral bodies posteriorly. The superior mediastinal contents include the thymus gland and great vessels, including the right and left brachiocephalic vein and the confluence of the internal jugular vein with each of these structures. It is through the superior mediastinum that the vagus, recurrent laryngeal and phrenic nerves descend into the mediastinum.

The superior mediastinum also accommodates the trachea and esophagus. As such, tumors and cysts in the anterior mediastinum can cause compression or invasion of surrounding venous and nerve structures (1-3).

From a surgical perspective, the superior mediastinum can be approached via cervical or anterior mediastinoscopy,

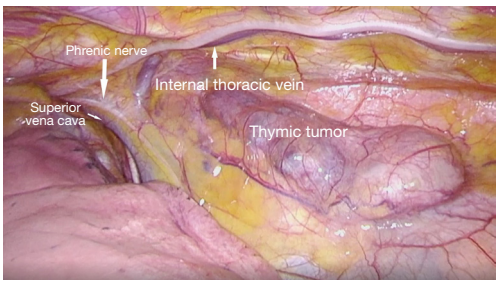

Figure 1 The view of the mediastinum as provided by VATS. Key mediastinal structures are noted. VATS, video assisted thoracic surgery.

as for lymph node sampling in lung cancer. It can also be approached from median sternotomy or from a lateral decubitus video assisted thoracic surgery (VATS) or thoracotomy, as for thymectomy.

During cervical mediastinoscopy, a mediastinoscope is inserted under the pretracheal fascia and along the anterior surface of the trachea. One major landmark for mediastinoscopy is the left brachiocephalic artery, which can be palpated anterior to the pretracheal fascia. The left brachiocephalic vein travels superficial to the artery, just behind the sternum. The internal jugular and subclavian veins meet posterior to the sternoclavicular (SC) joints to form the bilateral brachiocephalic veins. Importantly, the left brachiocephalic vein is 2 cm longer than the right, because it passes over the arch of the aorta to enter into the right sided superior vena cava (SVC). In turn, the brachiocephalic veins combine to form the SVC. At the right tracheobronchial angle, the azygous vein travels from posterior to anterior to drain into the SVC. The azygous vein from the mediastinoscope appears as a faint blue or green structure within the mediastinal fat just to the right of the takeoff of the right mainstem bronchus (4).

The SVC terminates in the middle mediastinum and joins the right atrium. The SVC forms the posterior boundary of the transverse pericardial sinus.

Approached from a median sternotomy, the most superficial structure to be encountered is the thymus gland. While the gland typically recedes in early adulthood, there are varying levels of remnant thymus gland in adults, and thymic masses can obtain size enough to account for compression of nearby structures. The veins of the thymus gland typically drain into the left brachiocephalic, the left internal thoracic, or the inferior thyroid veins. Approached via VATS for thymectomy (*Figure 1*), the junction of the left brachiocephalic vein and the SVC forms a useful landmark (4).

The vagus nerve leaves the skull and descends the neck posterior and lateral to the carotid arteries in the carotid sheath. Each nerve travels into the superior mediastinum posterior to the associated SC joint and brachiocephalic vein. The right vagus nerve enters the chest anterior to the right subclavian artery, where it gives off the right recurrent laryngeal nerve. The nerve then hooks behind the subclavian artery and ascends in the tracheoesophageal groove where it innervates the larynx. The right vagus nerve continues on behind the right brachiocephalic vein and branches into the right pulmonary plexus and right esophageal plexus. The left vagus nerve travels within the neck posterior to the common carotid artery. It then enters the mediastinum between the left common carotid and the subclavian arteries. At the left side of the aortic arch, it travels posteriorly behind the left phrenic nerve. It is separated from the left phrenic nerve by the left superior intercostal vein. The left vagus nerve then passes medially, where along the inferior aspect of the arch, it gives off the left recurrent laryngeal nerve, immediately lateral to the ligamentum arteriosum. The left vagus nerve travels inferiorly and gives fibers to the pulmonary and esophageal plexi.

The phrenic nerve originates from the C3, C4 and C5 nerve roots bilaterally and supplies the sensory and nerve fibers to the diaphragm. The phrenic nerve also supplies sensory fibers to the pericardium and mediastinal pleura. It enters the chest anterior to the subclavian artery. The left phrenic nerve frequently lies medial to the internal thoracic artery, and as such the left phrenic nerve is more susceptible to injury during sternotomy or thymectomy. Both phrenic nerves pass anterior to their respective pulmonary hila. The right phrenic nerve passes on the right side of the inferior vena cava (IVC), where it penetrates the diaphragm muscle near the caval aperture. The left phrenic nerve passes between the subclavian and common carotid arteries, crosses the medial surface of the arch of the aorta, and descends superficially along the pericardium. It then penetrates the diaphragm lateral to the heart. Additional branching of the phrenic nerve happens on the abdominal surface of the diaphragm.

Anterior mediastinum

The anterior mediastinum is the smallest subdivision and lies between the body of the sternum (below the angle of

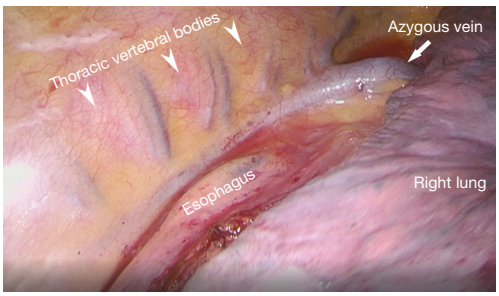

Figure 2 View of the posterior mediastinum encountered during right VATS. Key posterior mediastinal structures are noted. VATS, video assisted thoracic surgery.

Louis) and the pericardium. It consists of mostly fat, a few lymph nodes, loose connective tissue and branches of the internal thoracic vessels.

Middle mediastinum

The middle mediastinum is bordered by the pericardium anteriorly and posteriorly, the lungs laterally, the diaphragm inferiorly, and terminates superiorly at the level of the angle of Louis. It contains the heart, great vessel roots, as well as the trachea and main bronchi.

The trachea ranges from 10–13 cm in length and divides into the right and left mainstem bronchi at the carina behind the angle of Louis (5). The mainstem bronchi then join the left and right lung hila at the T6 and T4 levels, respectively.

Surface landmarks for the junction of the mediastinal veins will be discussed in a later section. The internal jugular and subclavian veins converge bilaterally into the brachiocephalic veins which then merge into the SVC. The IVC enters the chest through the diaphragm at T8 and joins the right atrium at the level of the sixth costal cartilage.

As mentioned previously, both phrenic nerves traverse the middle mediastinum before entering the diaphragm. The left phrenic nerve passes through the middle mediastinum over the left ventricle while the right phrenic descends to the right of the SVC, right heart border, and IVC. Both phrenic nerves then penetrate the diaphragm. The two vagus nerves run posteriorly to the mainstem bronchi, eventually branching into or contributing to the pulmonary and esophageal plexi. The cardiac plexus is additionally present within the middle mediastinum.

Posterior mediastinum

The posterior mediastinum is located inferior to the angle of Louis, anterior to the T5-T1 vertebrae, posterior to the left atrium, pericardium and diaphragm and between the parietal pleura of the lungs. It contains the thoracic aorta, the thoracic duct and lymphatics, posterior mediastinal lymph nodes, the azygous and hemiazygous veins. The thoracic sympathetic trunk lies lateral to the vertebral bodies and is often referred to as a posterior mediastinal structure.

The azygous veins lie lateral to the vertebral column and drain the back and thoracoabdominal walls as well as the mediastinal viscera. There is great anatomic variation in the course and caliber of these veins and their tributaries. The azygous and the hemiazygous vein usually arise posteriorly from the IVC or inferior renal vein.

The azygous vein establishes a collateral pathway between the IVC and SVC and drains the posterior chest wall and abdomen. *Figure 2* demonstrates the azygous vein as seen in the posterior mediastinum via a VATS approach to esophagectomy. It ascends through the posterior mediastinum, passing close to the right side of the bodies of the inferior 8 thoracic vertebral bodies. It travels over the esophagus, trachea, and right hilum to the SVC.

The hemiazygous vein arises by the junction of the left subcostal and ascending lumbar veins. It ascends laterally and to the left of the thoracic vertebral bodies and posterior to the aorta. It then crosses to the right side at the level of T9, posterior to the aorta and esophagus, to join the azygous vein.

The splanchnic nerves and the sympathetic trunks make up the bulk of the nerves in the posterior mediastinum. The sympathetic trunks comprise a large part of the autonomic nervous system. The thoracic trunks are in continuity with the cervical and lumbar trunks. The thoracic trunks lie in positions relative to their position in the thorax. They lie on the head of the ribs in the superior chest, the costovertebral joints in the mid chest and the vertebral bodies in the inferior chest. The lower thoracic splanchnic nerves supply fibers below the diaphragm. They consist of pre-synaptic fibers of the 5^{th}–12^{th} sympathetic ganglia, which pass through the diaphragm to supply the abdominal viscera.

Surface landmarks for vein connections

In addition to understanding the relation of the mediastinal

structures to each other, knowledge of surface markers for venous junctions proves useful in mediastinal surgery. The medial border of the sternocleidomastoid serves as a useful marker for the internal jugular vein. The internal jugular and subclavian veins merge to form the brachiocephalic veins behind the SC joints. The left brachiocephalic vein then crosses behind the manubrium to join the right brachiocephalic vein at the level of the first costal cartilage to form the SVC (6). To give an idea of the small space where these large veins combine, the average width of the manubrium is 4.9 cm in women and 5.7 cm in men (7). The azygous vein drains into the SVC at the level of the 2nd costal cartilage and the SVC joins the right atrium one interspace down at the right 3rd costochondral junction. Given the close proximity of the azygous to the cavo-atrial junction, dissection of this area should be done carefully to preserve the azygous for reimplantation later in an SVC reconstruction. The IVC enters the right atrium behind the 6th costochondral junction.

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Footnote

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Review Article

Penetrating cardiac injury: a narrative review

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Background and Objective: Penetrating cardiac trauma is rare but can cause life-threatening complications. Survival is dependent on prompt diagnosis and treatment. Given the low incidence and life-threatening implications, it is difficult to study in large prospective studies. The current literature regarding penetrating cardiac trauma comes primarily from large, experienced trauma centers and military sources. Understanding the history, current literature and even expert opinion can help with effectively treating injury promptly to maximize survival after penetrating cardiac trauma. We aimed to review the etiology and history of penetrating cardiac trauma. We review the prehospital treatment and initial diagnostic modalities. We review the incisional approaches to treatment including anterolateral thoracotomy, median sternotomy and subxiphoid window. The repair of atrial, ventricular and coronary injuries are also addressed in our review. The purpose of this paper is to perform a narrative review to better describe the history, etiology, presentation, and management of penetrating cardiac trauma.

Methods: A narrative review was preformed synthesizing literature from MEDLINE and bibliographic review from identified publications. Studies were included based on relevance without exclusion to time of publication or original publication language.

Key Content and Findings: Sonographic identification of pericardial fluid can aid in diagnosis of patients too unstable for CT. Anterolateral thoracotomy should be used for emergent repairs and initial stabilization. A median sternotomy can be used for more stable patients with known injuries. Carefully placed mattress sutures can be useful for repair of injuries surrounding coronary vessels to avoid devascularization.

Conclusions: Penetrating cardiac trauma is life threatening and requires prompt workup and treatment. Trauma algorithms should continue to refine and be clear on which patients should undergo an emergency department (ED) thoracotomy, median sternotomy and further imaging.

Keywords: Penetrating cardiac injury; cardiac trauma; cardiac injury repair; emergency thoracotomy

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Introduction

Cardiac injury previously was almost fatal, as described in the death of Sarpedon from an impalement of a lance to the heart in the Iliad (1). Hippocrates (2), Aristotle (3), Galen (4), Fabricius (5) and Boerhaave (6), all described such wounds to the heart as futile. While once universally fatal, penetrating cardiac trauma still has life-threatening implications. It is important to understand the how to promptly diagnose and manage these injuries to maximize survival. Despite advances in prehospital care, in-hospital protocols and surgical techniques patients can still

Table 1 The search strategy summary

Items	Specification
Date of search	03/25/2021
Databases and other sources searched	MEDLINE via PubMed, Google Scholar, University of Hawaii Libraries
Search terms used	"penetrating trauma"[MeSH]
	"polytrauma"[MeSH]
	"cardiac trauma"[MeSH]
	"penetrating cardiac trauma"[MeSH]
	"cardiac injury"[MeSH]
	"thoracic trauma"[MeSH]
	"emergency thoracotomy"[MeSH]
Timeframe	No exclusions were made based on date of publication
Inclusion and exclusion criteria	Focus was made on papers that address an aspect of history, incidence, etiology, presentation, diagnosis or treatment of penetrating cardiac injuries. Studies were excluded if they were small case studies. Studies written in primarily in English were given preference but studies with English translations were also included
Selection process	Review of articles was primarily done by Hromalik LR Jr but selection was made with approval of all authors
Any additional considerations, if applicable	Older texts found in introduction and that are not found on MEDLINE texts were found using University of Hawaii Library and Google Scholar

decompensate quickly with penetrating cardiac injuries. The purpose of this article is to better characterize the history and present treatment of penetrating cardiac trauma in the form of a narrative review. The rationale for creating this review is to combine the literature with expert experience to help guide future research and clinicians to better treat penetrating cardiac injury. We present the following article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-22-18/rc).

Methods

A narrative review was preformed synthesizing literature from MEDLINE and bibliographic review from identified publications as seen in the reference section. The search strategy is summarized in *Table 1*. Medical Subject Headings (MeSH) terms were used. Search terms included: penetrating trauma OR polytrauma OR cardiac trauma OR penetrating cardiac trauma OR cardiac injury OR thoracic trauma OR emergency thoracotomy. All abstracts were further screened by primary author Hromalik LR Jr. and qualitatively analyzed to include articles with penetrating cardiac injury. A focus was made on articles that presented an aspect of the history, incidence, etiology, presentation, diagnosis or treatment of penetrating cardiac injury. Papers were primarily in English but other texts were reviewed if there was an English translation available. Older texts and translations cited in the 'Introduction' and 'History' that are not primarily medical research were found utilizing Google Scholar and with review of texts at University of Hawaii Libraries.

History

The earliest interventions were described by Morgagni (7) in 1761 who described the compressive effects of blood by the heart. Larrey (8) was credited for pioneering the technique of a pericardial window. Ludwig Rehn performed the first successful repair of a cardiac injury on September 9, 1896 in Frankfurt (9). Exposure of the heart after penetrating trauma evolved at the turn of the century when Duval (10) first described the median sternotomy incision, while Spangaro (11) in 1906 described the left anterolateral thoracotomy incision. The diagnosis of cardiac injury evolved in 1926 when Beck described the Triad physiology

of cardiac tamponade. He also described an important repair technique that is still used today. This technique involves placing mattress sutures under the coronary vessels to spare ligation for lacerations to the heart (12,13). Treatment was then further developed by Harken (14) in 1946 who described the removal of foreign bodies adjacent to the heart and great vessels. Treatment was then extended beyond the operating room by Beall (15-18) who first described emergency department thoracotomy (EDT) and along with Cooley (17) who reported the potential benefits for cardiopulmonary bypass in the management of selected intracardiac injuries. Mattox (19-21) further protocolized the use of EDT and cardiorrhaphy including emergency cardiopulmonary bypass.

Incidence

Penetrating cardiac injuries are uncommon and represent a small fraction of penetrating trauma overall. Penetrating cardiac trauma is often described in high volume urban trauma centers (22-30). Iatrogenic penetrating cardiac injury can be also seen in any clinic or hospital, following procedures. Iatrogenic penetrating cardiac trauma is most often seen following pericardiocentesis. The true incidence of injury overall is difficult to quantify but various centers have described their experiences. Feliciano (22) described in a one-year experience 48 cardiac injuries at Ben Taub Hospital in Houston. Mattox (23) in 1989 described a 30-year experience from the same institution, reporting 539 cardiac injuries. Asensio (24,31) reported a total of 165 cardiac injuries within a 3-year period at LA County/USC hospital in Los Angeles. Tyburski (32) in 2000 reported an 18-year experience of 302 patients with penetrating heart injuries undergoing emergency thoracotomy. Seamon (26) described 207 cardiac injuries over 7 years between Temple University Hospital and the Hospital of the University of Pennsylvania. Clarke (28) described 206 cardiac injuries in South Africa over a 3-year period. The overall incidence varies by geographic location and is also influenced by violent crimes involving the use of firearms or penetrating objects (22-32).

Etiology

In the civilian setting, penetrating cardiac injuries are usually seen as a result of gunshot wounds and stab wounds. A subset of cardiac injuries are seen from iatrogenic needles, trocars, and catheters (33-39).

In the military setting, most patients do not survive cardiac injuries from high velocity automatic rifles in battle. The majority military reported injuries are from fragments of grenades or shrapnel. Rich (40) reported such injuries in 96 patients from the Vietnam conflict, arriving at treatment facilities. Hughes (41) describes over 2,000 thoracic injuries over 10 years during the Afghanistan and Iraq conflicts.

Clinical presentation

Most cardiac injuries from stab wounds will follow the trajectory of the insult. Gunshot wounds are different because they can cause injury from precordial and extra-precordial entrance sites (42). Hirshberg (43) described 26% associated cardiac injuries in 41 patients presenting with combined thoracoabdominal injuries, while Asensio (44) reported a 44% incidence of associated penetrating cardiac injuries in his series of 73 patients who sustained thoracoabdominal injuries.

Penetrating injuries to any of the cardiac chambers may quickly lead to acute cardiac tamponade and death. Hemorrhage through a lacerated pericardial injury will flow into the hemithorax and will lead to death. The pericardium can therefore prevent fatal exsanguination and allow patients survive long enough to reach the trauma center alive. They may have varying degrees of hemodynamic instability secondary to pericardial tamponade (24,31). Interestingly, the classic presentation of Beck's Triad (muffled heart sounds, jugular venous distension and hypotension) or Kussmaul's sign (jugular venous distension with inspiration) are only present in 10% of patients who present with pericardial tamponade (42).

Moreno (45) did a retrospective study that looked at 100 patients with penetrating cardiac injuries and reported higher survival 77% *vs.* 11% in patients who present with pericardial tamponade. Moreno also showed that right-sided chamber injuries confer a higher survival 79% *vs.* left-sided chamber injuries of 28% survival.

Diagnosis

The clinician should always be concerned for cardiac injury when patients present after sustaining any penetrating injury. If the patient is hemodynamically stable and has a widened mediastinum on chest X-ray the clinician should also have a high suspicion for cardiac injury. Sonography is an excellent tool that can determine the presence of

pericardial fluid. Physical exam findings of Beck's triad or Kussmaul's sign can also be supportive but not always present. Any injury with a concern of direct trajectory towards the heart should prompt preparation for a possible emergent bedside anterolateral thoracotomy should the patient acutely decompensate.

Subxiphoid pericardial window

The reliability of subxiphoid pericardial window technique *vs.* pericardiocentesis has been controversial in the evaluation and treatment of penetrating cardiac injury (46-54). These techniques may be useful in the absence of two-dimensional echocardiography. While these techniques might demonstrate hemopericardium, they are time consuming. In addition, a pericardial window may result in exposing a cardiac injury through a very small incision and may need a larger secondary thoracic operation. A transdiaphragmatic pericardial exploration at the time of a laparotomy (55) has been described in cases where patients have sustained combined thoracoabdominal injuries. Laparoscopic transdiaphragmatic pericardial window also has been described for more stable patients (56-58). However, if there is an injury found, they still may need a larger secondary operation for optimal exposure of the heart and treatment.

Two-dimensional echocardiography

Echocardiography has now become the gold standard in the initial diagnosis and evaluation of patients with penetrating thoracic injury. The diagnosis is made by looking for hemopericardium. It is fast, and easily reproducible (42,55,59-61). Governatori (61) performed a review of multiple studies that show echocardiography has a high accuracy up to 96–97% with sensitivity and specificity reaching near 100%. Echocardiography can also be used to further delineate some intramyocardial foreign bodies *vs.* missiles located within the cardiac chambers (62-64). We recommend use of sonography to look for pericardial fluid in all patients with concern for penetrating cardiac injury because it is fast, reproducible and can influence operative management.

Management

Patients with penetrating cardiac injury may have a fatal outcome regardless prehospital intervention. In the select group that are stable enough for transport to the trauma center, the time between initial injury and release of cardiac tamponade is of utmost importance. This prehospital course is marked by certain surrogate parameters for either improved or dire prognosis.

Under no circumstances should EMS personnel delay transport by insertion of intravenous lines—this should be carried out during transport. Concomitant notification of the trauma center to activate the trauma team is also of paramount importance (42). Gervin (65) demonstrated a survival advantage if patients are transported to the trauma center is within 9 minutes, while all patients succumbed when transport was greater than 25 minutes. Mattox (66) found no survivors in 100 patients who had received external cardiac compression for more than 3 minutes in the prehospital period and were not intubated. Lorenz (67) associated better survival if patients had systolic blood pressures of 60 mmHg or more in the field and upon arrival in the emergency department. Durham (68) showed the average survival was seen with 5 minutes or less of cardiopulmonary resuscitation, but this time improved to 9 minutes when prehospital intubation was performed.

Upon arrival to the emergency department, the trauma team should be ready to perform advanced trauma life support or immediately transport patients from the ambulance bay to the operating room (69). Patients can be grouped into multiple categories based on stability. The hemodynamically stable patient can allow time for expedited yet detailed workup. The unstable patient that responds to initial fluid resuscitation may have the opportunity to be transported to the operating room for a life-saving operation. Patients who present or go into cardiopulmonary arrest will require EDT (24,31,42,70,71). EDT, if performed under strict indications for cardiac injuries, has been shown to improve survival rate as much as 31% (72). Rhee (73) preformed a large systematic review looking survival after EDT with respects to location, mechanism of injury and signs of life on arrival. It was shown that patients with penetrating cardiac injury and with signs of life on arrival yielded the highest survival among those who underwent EDT. Seamon *et al.* (74) reviewed 72 studies of patients undergoing EDT. They compared outcomes by presentation for location, mechanism, pulse status, and signs of life. Signs of life were defined as: pupillary response, spontaneous ventilation, presence of carotid pulse, measurable or palpable blood pressure, extremity movement or cardiac electrical activity. They strongly recommend that EDT should be performed in patients who present pulseless

with signs of life after penetrating thoracic injury.

Techniques for cardiac injury repair

Incisions

Median sternotomy and left anterolateral thoracotomy are the two incisions of choice for cardiac injuries. The median sternotomy is preferred in patients who are treated for anterior stab wounds to the chest, and for those who arrive in some degree of hemodynamic instability, but stable enough for work up with sonographic or chest x-ray imaging. The left anterolateral thoracotomy is the incision of choice in the management of patients that arrive in extremis. This incision is also used as EDT for emergent resuscitative purposes (24,31,42,70,75). A bilateral transsternal anterolateral thoracotomy can provide optimal exposure of the mediastinum and both hemi-thoracic cavities if necessary.

Adjunct maneuvers

Exposure of the heart to repair posterior injuries can be accomplished in several ways. The Heart can be retracted using sutures. Temporary pledgeted sutures can be placed on the apex of the heart with the sutures cut long in order to slowly retract the apex superiorly to gain access to the posterior injury. Alternatively, a Satinsky clamp can also be used on the right ventricular angle to achieve the same exposure (76). A simple option that we recommend is to place folded wet towels sequentially behind the heart in order to gradually lift the heart up to provide exposure without causing the heart to go into an arrhythmia. Stabilizing devices can also be used to help provide exposure but require time to set up. It is important to be careful with placement of repair stitches on laceration injuries to avoid causing further tear injury.

Total inflow occlusion of the heart can also be performed by placing clamps on the intrapericardial location to isolate and repair injuries at the level of atriocaval junction. This will often cause the heart to fibrillate, requiring paddle defibrillation and pharmacologic intervention (42,75). It is important to remember that the heart should be intermittently compressed as cardiorrhaphy is performed in case defibrillation is necessary. Failure to decompress the heart before defibrillation can cause further injury to the heart.

Repair of atrial injuries

Exposure of atrial injuries is relatively straight forward. Right atrial injuries can usually be stabilized and controlled with a Satinsky clamp (77,78) followed by repair using 4-0 non-pledgeted polypropylene monofilament sutures. The atrium is thin walled and tears easily, so it is important to be gentle with traction of sutures to avoid further injury or tearing.

Repair of ventricular injuries

Blast injuries resulting from gun shots to the ventricle can damage the epicardium and myocardium making them more friable and unforgiving with standard suture repair. The repair can be further complicated by tachycardia or high-pressured bleeding. Left ventricle injuries will also have higher. Depending on the size of the injury, 2-0, 3-0 or 4-0 polypropylene can be used for repair. Many surgeons suggest that pledgeted sutures should be used for repair however they have not been demonstrated to have any benefit over a carefully placed suture in the horizontal mattress fashion. Commercial brand fibrin sealant (78,79) are also often recommended but have also not been proven to add any value or benefit over suture repair.

Coronary artery injuries

Direct coronary artery injuries can be challenging to repair. Proximal injuries will require cardiopulmonary bypass, especially if there is gross evidence of cardiac ventricular dysfunction. Distal coronary artery injuries can potentially be ligated. Specifically, if the distal third of the vessel is injured/lacerated there may be little benefit in bypass. Bypass may not be necessary if the heart remains without ventricular dysfunction and tolerates ligation. Off-pump bypass can also be an option in select patients (80). Cardiac injuries in close proximity to coronary arteries may be managed with carefully placed horizontal mattress sutures underneath the coronary vessel for safe repair, taking care not to narrow or occlude the coronary artery in the process (42,70,77,81-83).

Complex and combined injuries

These can be defined as penetrating cardiac injury in addition to associated thoracic, thoracic-vascular, neck, abdominal and abdominal-vascular, or peripheral vascular injuries. Priority should be given to treatment of injury with the greatest risk of blood loss or is most life-threatening (42,70,77,84-89).

Wall and Mattox (90) described complex cardiac injuries as those beyond lacerations of the myocardium. These injuries often include concomitant coronary artery injuries, cardiac valvular injuries, intracardiac fistulas, ventricular

false aneurysms and coronary sinus injuries. These may be addressed by the cardiac surgeon once the other life-threatening injuries are temporized and dealt with. Priority should always be limiting blood loss and stabilizing patient before definitive repair is undertaken.

Limitations

There are many limitations to this narrative review. First, this is not a systematic review of all research regarding penetrating cardiac trauma, and we do not specifically compare the overall quality of research included in our review. We have included relevant literature regarding the history, incidence, etiology, diagnosis, and treatment to provide guidance in the care of patients with penetrating cardiac injury.

Conclusions

Penetrating cardiac injury should prompt a quick comprehensive workup. Workup should include a sonographic exam that is useful to diagnose pericardial fluid indicating the need for operative treatment. In the hemodynamically stable patient, the workup can be more extensive and include CT imaging studies. An anterolateral thoracotomy can be used in the emergent setting to cross clamp the descending aorta in order to perform necessary cardiac repairs. A median sternotomy should be used in a more stable patient with identified cardiac injuries to optimize exposure and perform definitive repair. Our recommendations for exposure and repair techniques should be considered to optimize survival in all penetrating cardiac traumatic injuries. Future studies and policies should focus on refining trauma algorithms to include optimizing prehospital care and transport. Future research and policy should be driven with collaboration between high-volume, urban trauma centers that routinely care for penetrating cardiac injuries.

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Review Article

The evolution of anesthesia management of patients with anterior mediastinal mass

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Abstract: Anesthesia management of patients with mediastinal mass compressing the central airway is considered challenging. It is widely believed that general anesthesia induction in patients with mediastinal mass is associated with airway collapse, difficulty in ventilation and hemodynamic compromise. Additionally, several case reports and case series described patients demise after induction of general anesthesia. This has led to the strong recommendations to use inhalation induction, avoid the use of muscle relaxant and maintenance of spontaneous ventilation. Recent studies shed new light on our understanding of airway changes associated with mediastinal mass by directly visualizing and measuring the actual changes of the airway caliber and the variation in the peak inspiratory flow (PIF) and peak expiratory flow (PEF) in patients with mediastinal mass. These studies describe the changes in airway mechanics in different states e.g., awake and anesthetized, spontaneous and positive pressure ventilated with or without muscle relaxation. Interesting new findings in these recent publications show that general anesthesia with and without muscle relaxation does not worsen a pre-existing narrowing of the airway compressed by mediastinal mass. Moreover, it was discovered that the addition of positive pressure ventilation, positive end-expiratory pressure (PEEP) and muscle relaxation in an anesthetized patient were associated with improvement in the airway caliber and airflow in these patient's population. This new understanding of the mechanics of airway obstruction and the effects of anesthesia and mechanical ventilation on patients with mediastinal mass challenges our current anesthesia practices and leads us to consider a new approach to anesthetize and ventilate these patients. This article will review the past literature that led to the widely practiced current anesthesia techniques and how it is challenged with the new research. The author will also provide a new perspective and anesthesia technique that align with the new research findings for safe induction and maintenance of general anesthesia in patients with mediastinal mass.

Keywords: Mediastinal mass; anesthesia; airway collapse; muscle relaxant; hemodynamic collapse

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Introduction

Background

When an anesthesiologist encounters a patient with anterior mediastinal mass requiring general anesthesia, the concepts of airway collapse, vascular collapse (1,2), inability to ventilate, high airway pressures, and the possibility of patient's demise come to mind. Traditionally, inhalation induction, awake intubation, strong recommendations against the use of muscle relaxant and maintenance of spontaneous ventilation are all believed to be lifesaving anesthesia induction techniques (3-5). Due to the ever-present possibility of the patient's demise during anesthesia induction, the anesthesiologists are trained to always have a backup plan in the event of a catastrophe. Plan B includes, changing the patient position, rigid bronchoscopy, extracorporeal membrane oxygenation (ECMO) (6-9) and eventually waking the patient up from general anesthesia (10,11).

Rationale and knowledge gap

Literature search aimed at finding the origin of the above-mentioned complications associated with induction of general anesthesia and the anesthesia techniques recommendations to safely induce general anesthesia in patients with mediastinal mass, yields mostly case reports and a few case series. Case series and case reports do not compromise the highest level of scientific evidence. However, due to the gravity of the outcomes associated with anesthesia induction in patients with mediastinal mass, the case reports and case series with their author's plausible explanations of the cause of hemodynamic and ventilatory collapse, and recommendations for safe methods of anesthesia induction continued to be published and practiced (11). It is also important to note that, the rarity of encountering patients with mediastinal mass causing significant central airway compression has added to the inability to perform a systematic randomized study, as it would take years to have the appropriate sample size to reach a valid, significant conclusion.

Objective

In this article, historic data of case reports and case series and the new emerging data that contradict and/or attempt to explain the long-standing belief of the ventilatory and vascular collapse associated with anesthesia induction in patients with mediastinal mass will be reviewed. The author will also provide the culmination of 20 years' experience of managing the anesthetics of patients with mediastinal mass undergoing rigid bronchoscopy at a tertiary academic Cancer Center. Suggestions for future studies to better understand the hemodynamic and ventilatory changes in patients with mediastinal tumors undergoing general anesthesia will also be addressed.

Historical data

The earliest published recommendations for airway management of a patient with tracheal obstruction was a review article by Gordon in the *International Anesthesiology Clinics Journal* in 1972 (12). The author made the keen observation that the effective diameter of the trachea may be reduced to 3–4 millimeters before an otherwise healthy patient may complain of distress at rest. He also commented that the degree of the tracheal obstruction is influenced by volume and rate of air flow during ventilation, by phase of respiration, and by position in patients undergoing general anesthesia. Gordon provided the following recommendations for safe airway management in patients with mediastinal mass requiring general anesthesia:

(I) Preoperative assessment of the diameter of the obstructed tracheal lumen using chest X-ray films;
(II) Selection of an appropriate size endotracheal tube (ETT) based on the estimated tracheal lumen and advocated for the use of flexible armored ETT;
(III) Insertion of the ETT past the obstruction to secure the airway;
(IV) Direct bronchoscopic visualization of the tip of the ETT to ensure that the obstruction is bypassed;
(V) Introduction of the ETT over the bronchoscope in the event that difficulty is encountered in passing the ETT past the obstruction.

Gordons hypothesized that "In some cases, the induction of anesthesia and particularly the paralysis of the action of the voluntary muscles may result in collapse of the trachea and complete occlusion of the airway. In these circumstances, the anesthesiologist may introduce the ETT under topical anesthesia and during spontaneous ventilation in a conscious patient".

Gordon also recommended the avoidance of hyperventilation once the patient is intubated. He went on to explain that "patients with chronic obstruction of the trachea may have compensated respiratory acidosis and high $PaCO_2$. Hyperventilation will cause an abrupt and

significant reduction of the carbon dioxide resulting in metabolic alkalosis, which in some instances will result in the reduction of the cardiac output, collapse of the cardiovascular homeostatic mechanisms and cardiac arrest".

The earliest case report of airway management in a patient with mediastinal mass compressing the airway was in 1973 in the *British Journal of Anesthesia* (13). A 13-year-old who presented with increasing dyspnea, orthopnea, facial swelling, hypoxemia, and carbon dioxide retention leading to stupor. The patient was intubated awake with an ETT and difficulty with ventilation with high airway pressures was encountered. Bronchoscopy showed severe tracheal, carinal, and bilateral mainstem compression. As the compression of the right mainstem was less severe than the left mainstem, the reporting physician elected to place a longer ETT into the right mainstem. The patient was mechanically ventilated while he received 4 days of radiation therapy. Fortunately, the tumor decreased in size and the patient was successfully extubated. Interestingly, this early report of airway management in a patient with mediastinal mass compressing the airway was a successful management with a reported good outcome. In their discussion, the authors commented on the ventilatory parameters used during the mechanical ventilation of the patient stating that "in order to ensure complete expiration, however, an unusually long expiration time is necessary. In addition, marked hypotension may occur as a result of the high intrathoracic pressure, and the danger of progression to complete airway obstruction is always present". Even though the authors were able to manage the airway successfully and safely with intubation past the obstruction, they remained aware of Gordon's warning of complete airway collapse. The authors were the first to make the keen observation of air trapping, hyperinflation, and its effect on the hemodynamics. They were the first to recommend prolongation of the expiratory phase of respiration to avoid the air trapping.

The first case report of reverting to spontaneous ventilation when ventilation difficulty is encountered after muscle paralysis was a case report published in 1975 by Bittar *et al.* (14). In this case, a 19-year-old boy with lymphomatous superior mediastinal and chest wall mass was scheduled for excision of the chest wall mass. Preoperative chest film revealed tracheal and right main stem narrowing. Induction with thiopental and morphine caused apnea with difficulty to assist the ventilation manually. Succinylcholine infusion was started with no improvement in the ventilation. The succinyl choline infusion was stopped and adequate spontaneous ventilation was regained. The ventilation remained adequate and spontaneous with Face mask and nitrous oxide, morphine, and thiopental for the remainder of the procedure. 20 days later, the patient was scheduled for a staging laparotomy. Induction with thiopental, morphine, succinylcholine was uneventful. The patient was intubated with size 7 ETT. The peak airway pressure was 35 cmH_2O and the right hemithorax was not moving with ventilation and no breath sounds were detected on the right. The surgery was aborted, and the patient was awakened from general anesthesia to receive radiation therapy before another attempt at the surgery.

This case report emphasized and referenced Gordon's hypothesis that any trachea restricted by tumor may collapse and yield complete airway occlusion if the action of the voluntary respiratory muscles is paralyzed during induction of anesthesia. However, Bittar went on to recommend that "if evidence of central airway obstruction is found, surgery should be delayed till the lymphoma is irradiated and the tumor has shrunken". In his discussion, Bittar explained the mechanics of the central airway obstruction by stating "During spontaneous inspiration, the pleural pressure is negative to the atmospheric pressure. Inspiratory forces, therefore, exert a potential widening of the airways greater than that resulting from the increased elastic recoil (caused by increased lung volume) during inspiration. During expiration, the caliber of the airways decreases as lung volume decreases, but dynamic compression plays a significant role in further decreasing the caliber of the large airways, especially during forced expiration". Bittar also hypothesized that paralysis of the airway smooth muscle plays an additional role in the obstruction. In his conclusion Bittar stated that "It is conceivable, therefore, that the compromised airway in this patient remained patent during spontaneous ventilation, as a result of the basic mechanics of respiration. Similarly, because the skeletal muscles were paralyzed and the smooth muscles were relaxed during general anesthesia, airway obstruction occurred". It is noteworthy that, in this case report, the author encountered difficulty in ventilation before the succinylcholine infusion was started which is not completely explained by his hypothesis.

The first retrospective case series study of patients with Hodgkin's lymphoma who underwent surgical procedure between 1969 and 1973 was published by Hellman *et al.* in 1976 (15). In the late 1960s to early 1970s, patients with newly diagnosed Hodgkin's lymphoma were required to have exploratory laparotomy and splenectomy to

determine the stage and appropriate therapy of the disease. Retrospective review of 139 patients who underwent 203 procedures, of which 176 required endotracheal intubations were performed. Mediastinal and hilar masses were found in 74 of the 179 who underwent general anesthesia with intubation. Evidence of airway obstruction before surgery was found only in 19 out of the 74 patients. Difficulty in ventilation around the time of intubation was encountered in only 2 of these 19 patients. The first patient had tracheal deviation and right main stem narrowing and the second patient had narrowing of the right bronchus intermedius and the left main stem. In both cases the procedure was successfully completed after adjusting the ETT to bypass the obstruction. This case series highlights the rarity of encountering patients with significant central airway obstruction by a mediastinal mass and the fact that both cases were successfully managed without catastrophic outcome when the obstruction was bypassed by the ETT.

The first reported death on induction of general anesthesia in a patient with mediastinal mass was in 1981 (16). A 9-year-old boy who presented with subacute onset of dyspnea on exertion, orthopnea, fever, and acute syncope and cyanosis while bearing down with a bowel movement. Inhalation anesthesia induction with Halothane was performed in a semi sitting position. Despite adequate ventilation, the patient became cyanotic and bradycardic. Endotracheal intubation in the supine position ensued with no difficulty in ventilation. Chest compression and cardiopulmonary resuscitation (CPR) failed, and the patient progressed to asystole. Postmortem autopsy revealed a large mediastinal tumor encasing and heart and infiltrating the pericardium. It is important to note that, no difficulty in ventilation was encountered in this patient making the airway collapse an unlikely cause of death. This article drew attention to the importance of preoperative assessment of cardiac involvement in patients with mediastinal mass and its effect on the obstruction of the venous return and/or cardiac output. Syncope while bearing down heralds the detrimental effect of the increase in positive intrathoracic pressure while bearing down on the circulation. This should alert the anesthesiologist that such detrimental effect of positive pressure on the circulation is likely to be reproduced when positive pressure ventilation under general anesthesia is initiated.

Multiple case reports demonstrated the use of ECMO in patients with mediastinal mass undergoing procedures. One example is a case report by Landa *et al.* in 2021 where a 70-year-old male with a right para-tracheal mass extending into the anterior mediastinum and causing 90% tracheal obstruction required surgery for tumor debulking and tracheal stent placement (17). It was noted that the superior vena cava (SVC) was patent with no mass effect by the tumor. Preoperative left internal jugular and left radial artery catheters were inserted. Sedation with Ketamine was started before the surgeon cannulated the internal Jugular vein and left femoral vein and ECMO was initiated. General anesthesia was then induced with Ketamine and rocuronium, laryngeal mask airway (LMA) was placed, and pressure-controlled ventilation ensued. Bronchoscopy showed the 90% tracheal obstruction with adequate mechanical ventilation and stable hemodynamics. The tumor was debulked and a tracheal stent was placed before the ECMO was stopped, the patient was awakened and the LMA was removed. The authors highlighted the ECMO's ability to provide adequate gas exchange and hemodynamic support in patients with severe central airway obstruction requiring surgery. More interestingly, this article was the first report of a patient being adequately ventilated through an LMA despite a 90% tracheal obstruction. Emerging data in 2021 recommend the use of ECMO for cases of central airway obstruction and cardiac involvement (18,19).

Emerging data

First comparison of peak inspiratory flow (PIF) and peak expiratory flow (PEF) and tidal volumes in patients with extrathoracic upper tracheal stenosis during spontaneous and positive pressure ventilation through a laryngeal mask airway was published in an observational prospective study in [2008] (20). In this publication, 30 patients with post intubation or idiopathic laryngotracheal stenosis (average 3 cm below the vocal cord) requiring surgery to restore the lumen of the airway were studied. The patient's baseline spirometry and flow volume loops were recorded. General anesthesia with muscle relaxation was induced before a LMA was inserted. All patients were ventilated with a driving inspiratory pressure of 20 cmH_2O, respiratory rate of 10 and Inspiratory:Expiratory (I:E) ratio of 1:1 to minimize auto PEEP (positive end expiratory pressure). The patient's tidal volumes and flow volume loops under general anesthesia were recorded using the anesthesia machine monitor. The findings were

(I) Awake spontaneously ventilating patients had significantly low PIF and PEF with a more pronounced effect on the PIF, causing an increase in the PEF/PIF ratio (mean 2.4);

(II) When the same patient is placed under positive

pressure ventilation with muscle paralysis, there was a decrease in the PEF/PIF to a mean of 1 mostly due to improvement in the PIF with positive pressure ventilation with little to no effect on the PEF.

At their conclusion, the authors stated that "Spontaneous ventilation creates negative inspiratory intratracheal pressure that exacerbates an extrathoracic lesion, whereas positive-pressure ventilation generates positive intratracheal pressure that improves ventilation. This helps explain the apparent resolution of airway obstruction after positive-pressure ventilation". The successful use of 1:1 I:E ratio in this case series of patients with variable extrathoracic airway obstruction is due to the absence of air trapping as air flow limitation is more pronounced during inspiration than during expiration. Interestingly the author also concluded that "Positive-pressure ventilation through an LMA is an effective method of ventilating patients with laryngotracheal stenosis".

The most recent measurement of PIF and PEF in patients with anterior mediastinal mass undergoing noninvasive positive pressure ventilation was published in 2022 (21). In this report Fiorelli *et al.* recorded the peak inspiratory and expiratory flows in 13 patients with anterior mediastinal mass causing tracheal narrowing requiring stenting. The patients were in supine position with face mask applied and connected to a ventilator circuit. The flows were recorded while the patients were spontaneously ventilating and when non-invasive positive pressure ventilation (NIPPV) was applied with a PEEP of 10 cmH_2O. The authors' findings indicated that extrinsic tracheal compression causes impairment of the PIF > PEF with an increase in the PEF/PIF ratio. When NIPPV is applied there was an improvement in both PIF and PEF with a more marked effect on the PIF > PEF causing the PEF/PIF ration to decrease. These findings showed that positive pressure ventilation (NIPPV) with a PEEP of 10 cmH_2O exerts a modest increase in peak flows and a more pronounced effect on both inspiratory and expiratory volumes in an awake patient with central airway obstruction.

The first case report visualizing the increase in the airway diameter under general anesthesia with positive pressure ventilation was reported in 2018 by Hartigan *et al.*, in the *New England Journal of Internal Medicine* (22). In this case report a patient with an anterior mediastinal mass compressing the trachea, main stem bronchi and SVC was intubated awake. Video bronchoscopy was taken of the carina and the mainstem bronchi before and after administration of general anesthesia while the patient was in a sei-fowler position. The airway videos showed a decrease in the airway caliber after general anesthesia induction followed by an increase after muscle paralysis and the institution of positive pressure ventilation. Noteworthy, the addition of paralysis to the positive pressure ventilation did not confer further increase in the airway caliber indicating that the positive pressure incurred by the ventilation was able to expand the central airway caliber more than negative pressure during spontaneous ventilation. This was the first directly visualized evidence that positive pressure ventilation is superior to spontaneous ventilation in preventing airway collapse or decrease in airway caliber under general anesthesia. Interestingly, the author reported using ventilatory parameters during induction that mimicked the patient's ventilatory rate, volume and time while spontaneously ventilating. The authors hypothesized that mimicking the spontaneous ventilation mechanics would prevent air trapping that contributes to increased airway pressure and hemodynamic collapse previously reported with assisted ventilation. In the authors response to letters to the editor, they stated that "Airway caliber is affected by tracheal transmural pressures, which can be equivalently achieved by positive intraluminal or negative extraluminal (pleural) pressures". And that "Matching the volume-time ventilatory pattern of positive-pressure ventilation to that of spontaneous ventilation may also be protective".

First prospective observational study of bronchoscopic evaluation of airway caliber changes under general anesthesia and muscle relaxation in patients with central airway compression was published by Hartigan *et al.* in the *Journal of Anesthesiology* in 2022 (23). In this single center study, 17 adult patients (12 with anterior mediastinal mass, 1 with posterior mediastinal mass and 3 with both anterior and posterior mediastinal mass) were intubated awake in a semi-sitting position with 8.5 mm ETT or LMA after upper airway topicalization with lidocaine. A staged induction ensued while the compressed airway was continuously visualized by video bronchoscopy. Four ventilatory stages were studied: awake spontaneous ventilation, anesthetized spontaneous ventilation, anesthetized positive pressure ventilation, and anesthetized positive pressure ventilation after muscle paralysis. It is important to note that the authors maintained the same tidal volume, respiratory rate, and I:E ratio throughout the 4 phases being studied. The findings were:

(I) No significant changes were noted in the anteroposterior compressed airway diameter between awake spontaneous ventilation and anesthetized spontaneous ventilation. Most importantly, there was no reduction in the airway diameter after induction

of general anesthesia, positive pressure ventilation or the addition of muscle paralysis.

(II) There was a reported visual subjective improvement in the airway patency with the institution of positive pressure ventilation that persisted and further improved after muscle paralysis.

Reconciling the past and the present

Recent publications between 2018 and 2022 directly visualized and measured the actual changes in volumes, air flows and airway caliber in patients with obstructed central airway during inspiration, expiration with awake spontaneous ventilation, anesthetized spontaneous ventilation, and paralyzed mechanical ventilation. These newfound understandings explain the successful airway management and the causes of ventilation difficulties and catastrophic outcomes in the earlier case reports and case series between 1970s–1990s. In conclusions these findings are:

(I) *During awake spontaneous ventilation* in a patient with central airway obstruction, the negative pressure generated by inspiration causes widening of the central airway with an improvement of the inspiratory flow. During expiration, the airway narrows, and a prolonged expiratory phase enables the exhalation of the inspired tidal volume through the narrowed airway. These mechanics remain unchanged after the patients are anesthetized while maintaining spontaneously ventilating.

(II) *During anesthetized positive pressure ventilation*, the positive pressure of the inspiratory phase increases PIF and widens the central airway. Meanwhile, during the expiratory phase, the absence of positive pressure causes the central airway to collapse back to its narrow baseline, and the PEF remains unchanged resulting in air trapping, lung hyperinflation and subsequent hemodynamic compromise. Consequently, adjusting the ventilator settings to prolong the expiratory time or mimic the spontaneous ventilation volume, respiratory rate, and I:E is essential to recreate the prolonged expiration seen in awake spontaneously ventilating patients and allow for complete exhalation of the inspired tidal volume through the narrowed airway. A low respiratory rate can be an added advantage by allowing for more time to drive the inspiratory volume through the obstructed airway while maintaining prolonged expiration to prevent air trapping.

(III) *During anesthetized positive pressure ventilation with muscle relaxation*, it is clear from the recent studies that the administration of muscle relaxation in an anesthetized patient with central airway obstruction did not cause further changes in the PIF, PEF, or airway caliber making it a reasonable component of the general anesthesia plan in patients with central airway obstruction.

(IV) *The causes of hemodynamic collapse* encountered once the patients are anesthetized can be multifactorial and can be explained by

- (i) *Progressive air trapping* if the appropriate ventilatory parameters are not utilizedcan cause detrimental increase in the intrathoracic pressure with subsequent decrease in the venous return and cardiac output leading to hemodynamic collapse.
- (ii) *Tumor compression of the heart* causing mechanical obstruction of the venous return and cardiac output that can be worsened by the addition of positive pressure ventilation and hypovolemia. ECMO would be an ideal technique to maintain adequate circulation and tissue perfusion in patients with evidence of mechanical compression of the heart and its inflow and outflow tracts.
- (iii) *Hyperventilation* in patients with compensated respiratory acidosis causes rapid elimination of the carbon dioxide (CO_2) that can lead to respiratory alkalosis. Respiratory alkalosis causes intracellular shift of K and Ca, hypotension and impairment of cardiac function that may contribute to the hemodynamic deterioration.

Airway management for patients undergoing surgical resection

Adequate preoperative assessment of the location and degree of obstruction using computed tomography (CT) scan is essential. The size and the length of the ETT to be used should be selected to enable the passage through and past the area of critical obstruction. The use of armored ETT is recommended to avoid the external compression of the ETT by the tumor. Flexible bronchoscopy can be used to aid in the introduction of the ETT through the obstructed airway and to confirm that the tip of the ETT is past the obstruction.

Airway management for patients undergoing rigid bronchoscopy and stenting procedure

LMA or a rigid bronchoscope is more suitable airway devices for patients undergoing a procedure for central airway stent placement. The insertion of the LMA at the beginning of the procedure allows for complete examination of the entire airway, planning the stent size, length, location, and deployment of metallic stents. Meanwhile the rigid bronchoscope can be used to stent the airway open in patients with critical airway stenosis and ventilation difficulty. The deployment of silicon stents can only be achieved through the rigid bronchoscope.

Total intravenous anesthesia (TIVA) *vs.* inhalation induction

Historically, inhalation induction is the recommend anesthesia induction technique in a patient with mediastinal mass causing central airway obstruction requiring surgery. This recommendation is based on the belief that spontaneous ventilation should be maintained during induction of anesthesia to avoid airway collapse. It has clearly been shown in the above-mentioned reports that positive pressure ventilation is superior to spontaneous ventilation both in an awake and anesthetized patient due to its effect in widening the compressed airway and increasing the PIF during inspiration. Additionally, the use of muscle relaxant has been shown to cause a minimal increase or no effect on the airway caliber, PIF and PEF. In fact, the emerging data refute the fear of using intravenous induction with muscle relaxation.

Author's experience

In the author's practice at MD Anderson cancer Center, rigid bronchoscopy for airway stenting in patients with central airway obstruction is provided in the bronchoscopy suite as an outpatient procedure. A stepwise induction of general anesthesia and transition to positive pressure ventilation and muscle relaxation is commonly performed and was recently published in the *Anesthesiology News* Airway supplement in 2019 (24).

(I) Slow intravenous induction with propofol infusion in a semi sitting position to avoid acute changes in the hemodynamics associated with the administration of a propofol bolus.
(II) Continuous measurement of the tidal volume and airway pressure during induction by applying the anesthesia circuit's face mask to the patient to monitor for adequate air exchange.
(III) Muscle relaxation and positive pressure ventilation with an I:E ratio of 1:4 and low respiratory rate to avoid air trapping.
(IV) Insertion of the rigid bronchoscope past the obstruction area to stent the airway open and relief any air trapping during the anesthesia induction.
(V) In the event of hemodynamic compromise secondary to air trapping and the inability to pass the rigid bronchoscope past the obstruction, passing the flexible bronchoscope past the obstruction and applying suctioning can relief the air trapping and lung hyperinflation with restoration of the hemodynamics.

Future perspective

Based on the new literature describing the respiratory mechanics and airflow in patients with mediastinal mass, new guidelines and best practices of anesthesia induction and mechanical ventilation parameters are needed. Future studies should include analysis of the changes in inspiratory and expiratory tidal volumes, airway pressures, air trapping, auto PEEP and blood gas analysis in both awake and anesthetized patients with and without muscle relaxant. Identification of the most appropriate parameters and modes of mechanical ventilation, such as tidal volume, I:E ratios, PEEP, volume *vs* pressure-controlled ventilation, is essential to ensure hemodynamic stability under anesthesia.

Studies are also needed to compare the effects of inhalation induction and intravenous induction on the respiratory parameters during spontaneous ventilation. Additionally, reliable, reproducible actual measurement of airway caliber should be pursued to understand the correlation between different ventilatory settings, modes of ventilation and changes of the airway diameter.

In the author's opinion, the effect of the mediastinal mass on the ventilation should be studied. Positive pressure ventilation causes displacement of the membranous posterior wall of the tracheal and main stem bronchi, contributing to the increase in the central airway caliber during inspiration. Patients with posterior, lateral and/or bilaterally compressing mediastinal mass exhibit significant limitation of the movement of the posterior membrane that can be more challenging to ventilate than patients with anterior mediastinal mass. Further studies comparing

anterior, posterior, and lateral mass effect on the respiratory parameter and ventilation are needed.

Conclusions

This review article spans a long period of time of reports and research publications describing the anesthetic risks and management in patients with mediastinal mass. Our knowledge has evolved from scientific interpretation of the plausible causes of the patient's demise and airway complications associated with anesthetic management of these patients, to actual direct visualization and accurate measurement of the mechanics of the airway changes and respiratory restrictions associated with mediastinal mass. Proper utilization of positive pressure ventilation and muscle paralysis appear to confer wider airway caliber and better airflow in contradiction to our previous beliefs. The new knowledge leads us to consider a new perspective for the anesthesia management of patients with compromised airway secondary to mediastinal mass. Further research is needed to delineate the appropriate ventilation parameters, and best anesthesia practices to provide safe anesthetics in patients with mediastinal mass.

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Review Article

Review of the clinical outcomes of therapeutic bronchoscopy for central airway obstruction

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Abstract: Central airway obstruction (CAO) is a debilitating condition with a significant impact on patient's quality of life and risk of hospitalization from respiratory failure. The causes of CAO can be both benign and malignant. Benign CAO may be idiopathic or secondary to other disease processes (infection, intubation, tracheostomy, etc.). Malignant central airway obstruction (MCAO) may occur in patients with primary lung malignancy as well as metastasis from other malignancies including renal cell, colon, and breast. In a cohort review, MCAO was found in up to 13% of patients with newly diagnosed lung cancer. The obstruction may occur either due to endoluminal disease, extrinsic compression, or a combination of both. Several bronchoscopic tools are available to manage such obstruction. Practice patterns and tools used to relieve CAO vary between institutions and may depend on physician preference, patient characteristics, emergency nature of the procedure, and nature of the obstruction. To quantify the effect and added value of such interventions, it is crucial to understand the clinical impact these interventions have on patients. The clinical impact of therapeutic bronchoscopy (TB) must then be weighed against the potential complications to justify its value. Early studies of TB for CAO included patients with both malignant and benign etiologies. The study population's heterogeneity makes it difficult to determine how TB affects clinical outcomes, as clinical outcomes are disease specific. The impact of TB for a MCAO may be different when compared to a benign CAO. Similarly, the clinical outcome of treating an idiopathic benign CAO may be different than that of a post tracheostomy airway obstruction. In this article, we will focus on the clinical outcomes of TB in MCAO. TB has been shown to have a clear impact on weaning from mechanical ventilation, dyspnea, health-related quality of life, survival and quality adjusted survival. The potential impact of TB on these outcomes should be weighed against the potential risk of complications. Understanding the factors associated with improved clinical outcomes will help physicians decide when and if TB is helpful. Future studies should focus on creating a decision analysis tool to further define decision thresholds.

Keywords: Therapeutic bronchoscopy (TB); malignant airway obstruction; clinical outcomes

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Introduction

Central airway obstruction (CAO), defined as obstruction of the trachea and/or mainstem bronchi, is a debilitating condition with a significant impact on patient's quality of life and risk of hospitalization from respiratory failure (1). The causes of CAO can be both benign and malignant. Benign CAO may be idiopathic or secondary to other disease processes (infection, intubation, tracheostomy, etc.). Malignant central airway obstruction (MCAO) may occur in patients with primary lung malignancy as well as metastasis from other malignancies including renal cell, colon, and breast (2). In a cohort review, MCAO was found in up to 13% of patients with newly diagnosed lung cancer (3). The obstruction may occur either due to endoluminal disease, extrinsic compression, or a combination of both. Several bronchoscopic tools are available to manage such obstruction. For endoluminal disease, hot and cold ablative therapies as well as mechanical debulking may help reestablish patency of the airway (4). Airway stenting may be beneficial in cases of extrinsic compression. In cases of MCAO due to a combination of extrinsic and endoluminal disease, a combination of the aforementioned modalities may be used. Practice patterns and tools used to relieve CAO vary between institutions and may depend on physician preference, patient characteristics, emergency nature of the procedure, and nature of the obstruction (5).

To quantify the effect and added value of such interventions, it is crucial to understand the clinical impact these interventions have on patients. The clinical impact of therapeutic bronchoscopy (TB) may have must then be weighed against the potential complications to justify its value. Early studies of TB for CAO included patients with both malignant and benign etiologies (1,6-9). The study population's heterogeneity makes it difficult to determine how TB affects clinical outcomes, as clinical outcomes are disease specific. The impact of TB for a MCAO may be different when compared to a benign CAO. Similarly, the clinical outcome of treating an idiopathic benign CAO may be different than that of a post tracheostomy airway obstruction. In this article, we will focus on the clinical outcomes of TB in MCAO.

TB has been shown to have a clear impact on weaning from mechanical ventilation, dyspnea, health-related quality of life, survival and quality adjusted survival. The potential impact of TB on these outcomes should be weighed against the potential risk of complications. Understanding the factors associated with improved clinical outcomes will help physicians decide when and if TB is helpful. Future studies should focus on creating a decision analysis tool to further define decision thresholds.

Clinical outcomes

Clinical outcomes are quantifiable improvements in health, function, or quality of life following a specific intervention. Outcomes may be immediate (e.g., technical success), short term (e.g., dyspnea post procedure), or long term (e.g., quality-adjusted survival). Priority should be given to examining how an intervention affects patient-centered, clinically significant outcomes. Measuring the success of an intervention by merely the technical aspect of it may overestimate the true value of the intervention.

A more challenging question to answer is how much improvement in a particular clinical outcome following TB would justify its potential complications. While that may not be an easy question to answer, understanding the effect of TB on these clinical outcomes and the factors that may impact outcomes may help individualize the decision as to whether an intervention is warranted. Clinical outcomes that have been studied for TB in MCAO include technical success, weaning from mechanical ventilation, dyspnea, health related quality of life (HrQOL), survival, and quality adjusted survival.

Technical success

Technical success of TB, typically defined as reopening the airway lumen to >50% of normal, has been used as a primary outcome to assess its effectiveness (10). Ost *et al.* examined the technical success of 1,115 procedures on 947 patients. Technical success was achieved in 93% of procedures (10). Similar success rates were seen in other studies (11,12). The odds of technical success decreased with increase in the severity of the obstruction (13). Factors associated with success included endobronchial obstruction and stent placement. On the other hand, American Society of Anesthesiology (ASA) score 3, renal failure, primary lung cancer and left mainstem involvement were associated with failure. In a different study, distal patent airway on CT scan and during bronchoscopy, non-smokers, and decreased time from radiographic finding of CAO to intervention increased the likelihood of technical success (13,14). The likelihood of technical success of TB was not significantly different between centers using different techniques and there was no single best method

in terms of ablative techniques (10). Stenting was found to be associated with a higher technical success. This finding, however, should be interpreted with caution as it may not necessarily be a causal association and may be confounded by indication (Physician may decide a stent is of no value in a patient with extensive disease that goes beyond the central airways). In addition, the technical success of stenting must be weighed against the risks of long-term complications that may arise from keeping the stent (15). In the study by Ost *et al.*, those whom dyspnea scores were measured, clinically significant improvement in dyspnea occurred in 48% of patients. This suggests that technical success of TB does not always translate into clinical improvement (10).

Weaning from mechanical ventilation

Patients with MCAO may develop respiratory failure requiring intubation and mechanical ventilation. The ability of TB to allow for a rapid weaning from the ventilator is an objective short-term outcome that has been assessed in prior studies. Colt *et al.* retrospectively reviewed 32 patients with MCAO. Of the 32 patients, 19 patients were mechanically ventilated. Bronchoscopic intervention allowed immediate discontinuation of mechanical ventilation in 10 (52.6%) (16). Murgu *et al.* examined the outcomes of 12 consecutive intubated and mechanically ventilated patients with inoperable or unresectable CAO from non-small cell lung cancer (NSCLC). TB resulted in immediate extubation in 9 patients (75%) (12). These studies demonstrate the impact of TB on the ability to wean patients with malignant CAO from the ventilator. Weaning from mechanical ventilation may allow for time for additional systemic treatment and provide time for the patient to discuss further goals of care.

Dyspnea

Dyspnea is the main symptom of MCAO and may result in sleep impairment, increase fatigue, and decrease functional performance (17). Improvement in dyspnea can be measured via standardized scoring systems including Borg score, San Diego Shortness of breath questionnaire or via a visual analog scale (10,17-19). Objective improvement in dyspnea using forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and 6-minute walk test (6MWT) has also been demonstrated (20). Overall, TB for MCAO has been shown to improve dyspnea in 48–75% of cases depending on the patient characteristics, nature and location of the obstruction (19,21,22). Various factors have been found to be associated with increased likelihood of improvement in dyspnea. In a retrospective study of 301 therapeutic bronchoscopies, a visible distal airway on CT and shorter time to intervention from radiographic CAO were associated with increased success rate (13). Ong *et al.* found that a higher baseline Borg score was associated with greater improvement in dyspnea (11). Similarly, greater baseline dyspnea was associated with improvement in dyspnea, whereas smoking, having multiple cancers and lobar obstruction were associated with smaller improvements (10). These findings suggest that significant functional impairment due to shortness of breath should not preclude bronchoscopic intervention provided that there is significant dyspnea, dyspnea is likely caused by the airway obstruction and that dyspnea is impacting the patient's functional status. Stenting the esophagus as well as the airway in cases of esophageal malignancy has also led to improvement in both dysphagia and respiratory symptoms. The lack of comparator limits the ability to clearly measure the value of double stenting (23).

Dutau *et al.* assessed the impact of silicone stent placement after successful TB in symptomatic MCAO without extrinsic compression and concluded that silicone stent placement maintained the benefit of the TB after one year on dyspnea score as well as obstruction recurrence, although data should be interpreted carefully as the study was not able to recruit the target number (24).

HrQOL

HrQOL is a multifaceted outcome that incorporates physical, mental, emotional, and social function. This outcome is broader and is not solely dependent on dyspnea (17). HrQOL is frequently measured by various questionnaires and scales including European Organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30), 36-item short form survey (SF-36), and SF-6D HrQOL (10,11,18,25). Initial studies examining the impact of TB on quality of life were small, and did not find a significant improvement in HrQOL. Amjadi *et al.* in prospective study of 24 patients found that while dyspnea scores improved in 85% of patients, HrQOL, measured by the EORTC did not change for the group as a whole (17). Similarly, Oviatt *et al.* did not find a significant difference overall in HrQOL measured in 19 patients who underwent TB for MCAO despite 84% of patients maintaining airway patency (20). However, larger studies have demonstrated HrQOL improvement after TB

for MCAO in both prospective and retrospective fashion (10,11,17,26). A retrospective study of 1,115 patients by Ost *et al.* found that Greater baseline dyspnea was associated with improved HrQOL whereas lobar obstruction was associated with smaller improvements (10). The data for HrQOL was only available in a subset of patients (183 patients) from select centers, therefore generalizability of these findings may need to be verified. In addition, retrospectively assessing the impact of TB on HrQOL can be confounded by indication, as the intention of a TB may be to avoid future potential worsening of an airway obstruction rather than for immediate relief. In the former case the impact on HrQOL may not be significant.

Survival

Survival is a longer-term outcome when compared to dyspnea. It is one of the most important outcomes when evaluating any drug, intervention, or procedure in oncological clinical trials (27). This outcome is clear, unambiguous, and unbiased. When MCAO is managed with TB, survival is reported to be no different compared to patients with advanced NSCLC without MCAO (28). When compared with patients with MCAO who refused TB, patients who underwent TB had a longer survival after matching for age, comorbidities, type of malignancy and type of obstruction (4±3 and 10±9 months respectively) (25). The impact of specific tools on survival has been evaluated. Brutinel *et al.* found that laser resection improved survival when compared to historical controls that received radiation (40% mortality at 7 months and 72% at 1 year compared to 76% and 100% respectively) (29). Similarly, Macha *et al.* sought to evaluate the impact of endobronchial laser resection in addition to radiation therapy on survival in 75 patients with MCAO and compared them to a retrospective cohort that received external radiation alone for the same indications. Laser resection did not influence the overall survival, however, in patients who had complete recanalization, survival was prolonged by more than 4 months compared to those whom recanalization failed, although the risk of bleeding was higher (30). Desai *et al.* found no difference in survival between patients who received laser plus radiotherapy compared to those who received radiotherapy alone, although significant increase in survival was noted in patients who underwent emergent laser compared to emergent radiation in patients with critical MCAO (31). Stratakos *et al.* in a prospective study showed a significant improvement in survival in patients who underwent TB compared to those who declined the intervention after matching for comorbidities (10±9 and 4± 3 months respectively) (25). This may be due to the potential improvement in their functional status which would allow patients to receive further anti-cancer therapy.

Additionally, the effect of stenting on survival has been studied. Saji *et al.* retrospectively reviewed 65 patients with MCAO that underwent airway stenting. Airway stenting provided acute relief of symptoms, although overall survival was not significantly changed (32). While Razi *et al.* found that timely stenting was associated with improved survival in patients with intermediate and poor performance status when compared to historical controls (33). Other studies suggested that stenting was associated with worse survival (14,22). Given the retrospective nature of the majority these studies, these results may be confounded by indication (e.g., stents may not be placed when the disease is very extensive) and therefore results should be interpreted with caution.

Poor survival following TB was associated with underlying chronic pulmonary disease, poor performance status, extended lesion, extrinsic or mixed lesion as well as not receiving adjuvant treatment following bronchoscopic intervention (34). Patients who underwent additional adjuvant treatment following TB, and those with obstruction limited to one lung seem to have better survival (34,35). Guibert *et al.* retrospectively studied data from 204 patients and concluded that reduced survival was associated with high American Society of Anesthesiologists (ASA) score, non-squamous histology, and metastatic tumors (36). A distinction between patients with high ASA due to CAO and those due to other organ dysfunction should be made, as patients with high ASA due to CAO seem to benefit from TB (36).

Quality adjusted survival

Quality adjusted survival is an important indicator to assess the cost-effectiveness of an intervention and the true impact on quality of life (37-41). Although TB may prolong life, most patients benefit from the improvement in quality of life during that time. Quality-adjusted life day is calculated as the area under the utility curve with time on the x-axis and quality of life on the y-axis (42). The impact of TB on long term quality-adjusted survival has not been studied until recently. Ong *et al.* performed a prospective observational study of 102 consecutive patients with MCAO that underwent TB. The median quality adjusted survival was 109 quality-adjusted life-days. Factors associated with

longer quality-adjusted survival included better functional status, treatment naïve tumor, endobronchial disease, less dyspnea at baseline, shorter time from cancer diagnosis to TB, absence of cardiac disease, bronchoscopic dilation, and receiving chemotherapy post intervention (11).

Complications

Although proven to be very effective in treatment of MCAO, TB is not without complications. Reported complications and adverse events are bleeding, pneumothorax, worsening hypoxia, remaining on the ventilator, airway injury, and stent related complications (18,22,43). The overall complication rate of TB for MCAO is reported to be 3.9%. Procedure-related death has been reported between 0.5% and 1.3% (22,34). Moderate sedation, high ASA, urgent or emergent bronchoscopy, and redo bronchoscopy were associated with increased risk of complications (22).

Conclusions

TB for MCAO should be considered as part of the multimodality approach to the management of the disease due to its overall positive impact on dyspnea, survival as well as long term quality of life. However, it is clear based on the available data that not every patient may benefit from such intervention, and the procedure is not without risks. Therefore, it is important to take into account the likelihood of technical success, the potential impact of technical success on dyspnea and how long is that impact expected to last, and how that will ultimately affect long-term HRQOL. The potential benefits should then be weight against the potential complications of the intervention. Understanding the factors associated with improved clinical outcomes will help physicians decide when and if TB is helpful. Future studies should focus on creating a decision analysis tool to further define decision thresholds.

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Footnote

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Review Article

Airway stenting for central airway obstruction: a review

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Abstract: Central airway obstruction is a serious complication of various diseases, most often malignancy. Malignant etiologies include primary lung cancer as most common though metastases from various other cancers can obstruct the airways as well. Benign etiologies include inflammatory or fibrotic changes due to prior airway interventions (e.g., endotracheal intubation or tracheostomy) or specific autoimmune conditions. Different interventional modalities exist including various electrosurgical or mechanical debulking tools, though these are sometimes insufficient or contraindicated for the purpose of restoration of airway patency. The placement of stents is thus needed in certain particularly complex or refractory cases. Airway stenting requires careful patient selection and stent selection along with a thorough knowledge of relevant anatomy and procedural technique. Indeed, certain clinical presentations are better suited for stent placement and more likely to achieve a symptomatic benefit. Moreover, a variety of stents exist with each having different attributes that may better fit specific conditions. Complications must be managed properly as well. These include stent migration, granulation tissue formation, and stent-related infection which can have clinically significant consequences. In this review, we will discuss airway stenting for central airway obstruction with regard to these various subject areas as well as conclude with discussion of future research directions.

Keywords: Airway obstruction; stenosis; stent; bronchoscopy; interventional pulmonology

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Introduction

Central airway obstruction refers to blockage of the trachea and main stem bronchi (1). The lobar bronchi are sometimes incorporated by this definition (2). Malignant causes are most often lung cancer though other malignancies metastatic to the lung can also lead to airway obstruction. Non-malignant causes include post-intubation or post-tracheostomy stenoses or those related to post-lung transplant healing; defects in the airway wall and autoimmune disease can also lead to this (3).

Various interventions for central airway obstruction exist in the armamentarium of the interventional pulmonologist, including ablative tools, mechanical debulking, and airway stents. The latter are typically employed when more conservative techniques have proven inadequate. In addition, stenting requires appropriate training and experience which then allows the proceduralist to properly select patients and the stent to be employed. Expertise in this area also prepares the physician to foresee and manage complications.

In this article, we will review airway stenting for central airway obstruction, with particular attention to the indications and patient and stent selection. We will also review the more apropos data in the literature regarding stents and their outcomes, including complications. We will then conclude by discussing new research horizons in this field.

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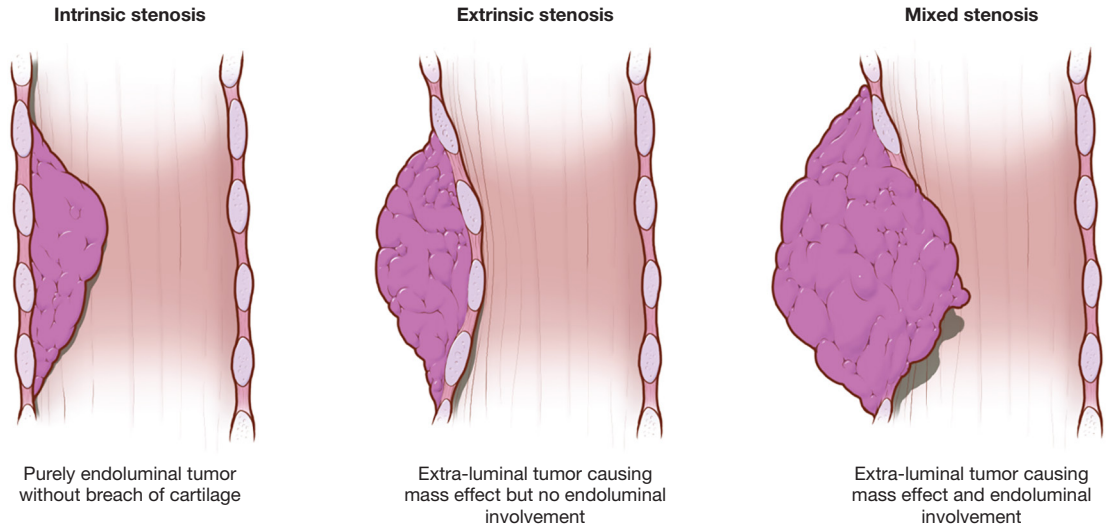


Figure 1 Some of the various manifestations of central airway obstruction. In this depiction, this is due to mass effect by tumor.

Indications

The most common indication for stenting is airway obstruction. This can present in three main fashions: intrinsic or endoluminal, extrinsic or extraluminal, or mixed (*Figure 1*). Purely intrinsic obstruction, typically due to malignancy, can often be managed with bronchoscopic interventions. However, stenting may still be required if significant tumor burden remains despite endoluminal therapies or if tumor regrows rapidly. Purely extrinsic obstruction due to compression by masses outside the airway require stenting because there is nothing to intervene upon within the airway lumen. A mixed presentation can also occur in which there is both intrinsic and extrinsic pathology. This often requires a combination of modalities to restore adequate patency to the affected airway and may requiring stenting if the extraluminal compression is found to be significant after the endoluminal component is cleared.

Another indication is weakness of the airway wall such as in tracheobronchomalacia in which the airway wall collapses to variable degrees. Defects in the airway wall such as airway fistulae (due to cancer or trauma, for example) or anastomotic dehiscence after lung resection or transplantation may also require a stent to bridge these gaps.

A much less common indication for stenting is when bleeding control with tamponade of an airway wall is needed. This has been typically done in the setting of diffuse airway wall bleeding such as due to tumor infiltration (4). Endoluminal ablative therapies can be used but a stent is a rapid intervention that can cover a wide area of disease relatively quickly.

Patient selection

Ultimately, the choice of whether to place an airway stent in a given patient depends on the risk/benefit ratio for the presenting clinical scenario. Several factors must be taken into consideration simultaneously.

Firstly, the exhibiting airway obstruction must be of sufficient severity as to explain the patient's symptoms. Patients often have multiple potential reasons to have dyspnea and it may be that airway obstruction is a less likely culprit in a given case. For example, a longtime smoker presenting with mild airway obstruction from newly-diagnosed lung cancer is also at risk for and may concurrently have chronic obstructive pulmonary disease, pulmonary embolism, and/or cardiovascular disease. If the airway involvement in such an instance is not significant then one of these other factors (or a combination) may be the etiology for dyspnea in which case stenting will not be beneficial. It is generally held that central airway lumen must be reduced to approximately 50% of normal before a patient will develop symptoms (1). A tracheal diameter of 8 mm usually will lead to dyspnea on exertion. Reduction to 5 mm or less will lead to dyspnea at rest (1). In such cases, airway intervention should be considered, even if other contributing etiologies may also be at play.

Secondly, timing is a factor. In cases of severe obstruction,

bronchoscopic intervention should be performed promptly. However, in certain cases where observation at the present time may be a reasonable plan (due to borderline severity of airway obstruction, for example), one must also consider whether delaying intervention will lead to a more challenging or risky procedure later. In those situations, it may be more prudent to intervene sooner rather than later.

Another consideration is whether bronchoscopy is the best intervention for a given case that clearly does require some form of intervention. In some instances, such as lymphoma or small cell lung cancer, for example, chemotherapy and/or radiation may improve airway obstruction relatively quickly and non-invasively. Any patient in extremis from severe airway obstruction requires bronchoscopy immediately, of course. Bronchoscopy and stenting likely would also be indicated in cases where a patient's disease has been refractory to other therapies and a stent is the only remaining option to relieve symptoms. In cases of tracheobronchomalacia, surgery is the treatment of choice but stents are used as a trial intervention to ensure that restoration of airway lumen leads to symptomatic benefit (5). As such, this is a case where a stent is not the ideal choice but is a necessary temporary measure.

Finally, a few other factors are necessarily part of the risk/benefit comparison and these potential issues also need to be taken into account. Complications are not very common with airway stents but they do occur, some in the near-term but more in the longer-term (see section on '*Complications*' below for more details). A given patient's capacity to tolerate these complications (e.g., infection, stent migration) must be considered. From a sedation perspective, stents usually require bronchoscopy under general anesthesia and a patient's ability to tolerate this needs to be incorporated in the decision-making process. Some patients with malignant central airway obstruction have a rather limited life expectancy and their goals of care need to be considered, including their willingness to undergo invasive procedures. It must be emphasized, however, that airways stents can certainly be palliative and helpful for relieving dyspnea even at the end of life (6). From a procedural technique perspective, there must be patent airways distal to the obstruction. Otherwise, stenting will be futile, opening part of an airway only to lead to obstruction distal to that. This may be ascertained by pre-procedural imaging but is not always clear until the time of direct visualization by bronchoscopy.

Importantly, aside from these important concepts, there are data to help guide the patient selection process. As part of the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education (AQuIRE) registry, Ost and colleagues collected and analyzed data from 1,115 bronchoscopies performed on 947 patients for malignant central airway obstruction at 15 different centers with 26 physicians (2). Central airway obstruction was defined as ≥50% occlusion of the trachea, mainstem bronchus, bronchus intermedius or lobar bronchus. There were statistical differences in practice patterns between the centers with regard to anesthesia, ventilation, rigid bronchoscopy, ablative techniques and stent use. Approximately one-half of patients had any endobronchial obstruction and nearly one-half had mixed obstruction; one in seven patients had any extrinsic obstruction. Over one-third of cases involved an airway stent for recanalization. In terms of outcomes, 93% of procedures were technically successful (defined as reopening the airway lumen to >50% of the normal diameter and connecting to a viable area of distal lung) and stent use was associated with higher rates of technical success. Notably, after therapeutic bronchoscopy, patients with worse baseline dyspnea (based on the Borg scale) had greater improvements in both dyspnea and health-related quality of life. Those with higher American Society of Anesthesiology score (an assessment of overall health) and poorer functional status had greater increases in health-related quality of life. As such, the patients that are often thought to be at greatest risk for these procedures may be the very ones that stand to gain the most from them. Additionally, patients with non-lobar obstruction also had greater improvements in both dyspnea and health-related quality of life. This is particularly relevant to the practice of stenting because stents are more-readily placed in larger airways than in lobar bronchi, there are more options commercially available for airway stents for these more central airways, and there is much more experience in the field of bronchoscopy with stenting in these locations as compared to lobar stents.

In all, several factors need to be taken into account when determining whether to intervene in a case of airway obstruction—and whether a stent is the best option therein. Other etiologies for a patient's symptoms, timing, ability to tolerate complications, severity of symptoms and location of obstruction, among others, all must be synthesized and carefully weighed.

Stent selection

The ideal airway stent would have several characteristics (7).

Firstly, it should be relatively easy to implant. It also must be able to be readily removed once it is no longer needed while simultaneously adhering to the airway well enough that it stays in place and does not migrate spontaneously. The diameter needs to be large enough to restore maximal patency but not so large as to possibly cause tissue ischemia. Preferably, flexibility will allow it to be placed into a narrowed airway and also accommodate physiologic airway movement (e.g., as occurs with coughing and respiration) yet also have sufficient radial force to counteract airway obstruction. Finally, it must also harmonize well enough with a given patient's anatomy such that granulation tissue is minimized (see '*Complications*' section below for further discussion) but not match the anatomy of a compressed airway so much that it simply replicates the obstruction. As such, the more personalized or customized a stent can be, the more likely it is to be a benefit to a patient rather than a detriment. Indeed, stents need to be as carefully selected as possible so as to not make a patient's situation worse rather than better.

An assortment of airway stents are commercially available, usually categorized based on the material with which they are made—metal or silicone. They are sometimes further subcategorized based on shape and can have distinct advantages or disadvantages depending on the clinical indication (*Table 1*). Generally speaking, metal stents are easier to place than silicone stents and can be done via flexible bronchoscopy alone (without requiring rigid bronchoscopy). They also can mold or conform to a given airway fairly well and tend to migrate less often than silicone stents due to their design. Silicone stents are easier to remove, can be customized to a degree at the time of procedure, and are less costly than metal stents. Below we will review a representative sample of the available and most recent data on the use of airway stents for central airway obstruction.

Metal stents

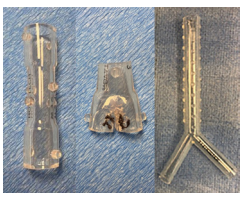
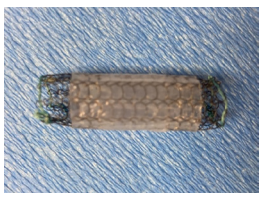
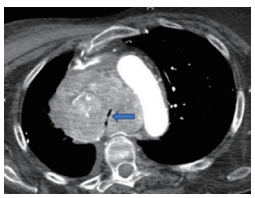
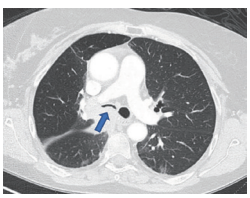
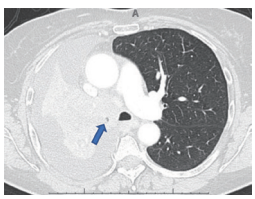
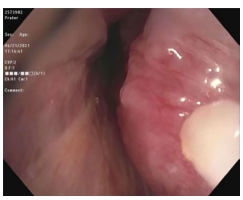
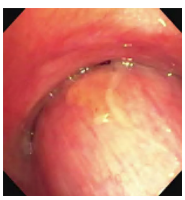
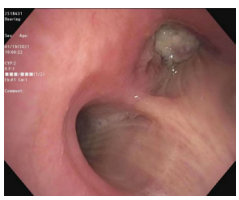
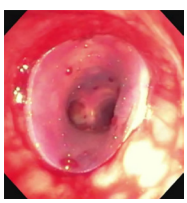
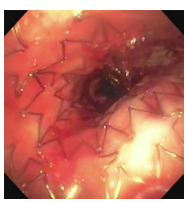
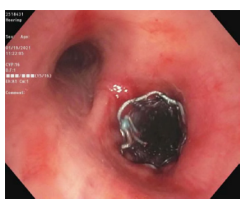
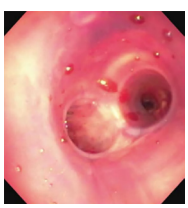
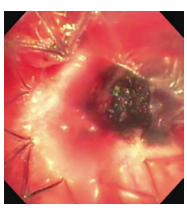
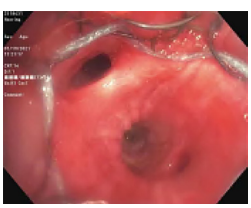
Metallic stents were initially developed approximately four decades ago and gained favorable attention for some time. However, possibly because use outpaced knowledge of how to prevent and manage complications, a prevalence of poor outcomes were observed, and the Food and Drug Administration (FDA) administered a black box warning for the use of metallic stents in benign airway disease (8). As a result, a decline in the practice resulted for some time. The history surrounding this as well as the evolution of subsequent generations of stents has been reviewed extensively by Avasarala (9). Indeed, as stent technology has advanced over the years with progressive improvements in their design, there has been a resurgence in their application over the last several years.

The original metallic stents were made of stainless steel or tantalum. More modern stents are made of nitinol, a metal alloy of nickel and titanium. Initially developed by the military in the late 1950s, it has since found a variety of applications including in electronics, civil engineering, and even the automobile industry (10). Nitinol has two important properties that make it particularly useful for recanalization of obstructed airways. Shape memory allows it to take on a deformed shape below a certain temperature and even to retain that shape when the external force is removed (10). However, once it is heated above its 'transformation temperature', it returns to its original, undeformed conformation (hence the term, 'self-expandable metallic stent' or SEMS). This allows stents to be compressed and placed into a deployment system that can be inserted into a narrowed airway and then expand to the intended size at body temperature once deployed. Secondly, superelasticity allows the stent to withstand significant amounts of strain (e.g., from coughing) as well as to conform to the shape of a given stenosis (11,12).

Metal stents now are typically produced either covered by a membrane or uncovered. The latter are completely porous, akin to a mesh or chain-linked fence. As such, they are not appropriate for malignant endobronchial obstruction in which case surrounding tumor would simply grow into the stent. But these can be successfully used for anastomotic dehiscence after lung transplantation, for example, as the formation of granulation tissue along the uncovered stent can help seal the defect. Covered stents typically employ polyurethane or silicone membranes. These membranes cover the stent and thereby prevent tumor in-growth. A disadvantage of this is that mucociliary function underneath the covering is compromised and also, in the case where an obstruction traverses a side-branch airway, that airway will be obstructed by the stent. Metal stents that are covered with silicone have been termed 'hybrid' stents because they are composed of both metal and silicone. The Bona stent (Thoracent, Huntington, NY, USA), Aero (Merit Medical Endotek, South Jordan, UT, USA) and Ultraflex (Boston Scientific, Marlborough, MA, USA) stents are such hybrid stents and are also among the more popularly used.

There are several series that have been published over the years and a representative sample will be discussed

Table 1 Comparison of three typical stent types with cases in which they were employed to relieve central airway obstruction

	Dumon Silicone (A)	Aero self-expandable metal fully covered (B)	Ultraflex self-expandable metal partially covered (C)
Advantages	• Easy to remove • Available in Y, tube, and hourglass shapes • Customizable at procedure time	• Easier to place (no rigid bronchoscopy) • Can adapt to irregular anatomy • No risk of tumor ingrowth since fully covered	• Easier to place (no rigid bronchoscopy) • Can adapt to irregular anatomy • Uncovered ends allow ventilation and may help prevent migration
Disadvantages	• Requires rigid bronchoscopy • Increased risk of granulation	• Possible increased risk of infection • Lack of uncovered portion does not allow ventilation	• Uncovered ends may allow tumor ingrowth and make removal more difficult
Stents			
Pre-intervention CT			
Pre-intervention bronchoscopy			
Proximal end of stent			
Distal end of stent			

(A): Silicone Y stent placed to relieve critical tracheal obstruction. The trachea is reduced to a narrow slit (arrow). Different silicone stents are shown: hourglass, hourglass customized into mini-Y, and Y stent. (B): Aero stent used to treat severe extrinsic obstruction (arrow) of the right main stem bronchus from a mass compressing the posterior membrane of the airway. (C): Ultraflex stent used to relieve obstruction of the right main stem bronchus which has been compressed down to a pinhole (arrow). There is resultant complete post-obstructive collapse of the right lung. CT, computed tomography.

here. A large series of 376 metallic stents was described by Sinha and colleagues (13). All were placed to manage post-transplant complications, mostly bronchial stenosis with a minority being for anastomotic dehiscence. Slightly over half of the cases employed the Bonastent, with the remainder using the Atrium iCast (Atrium Medical, Hudron, NH, USA) or Aero stents. Median individual stent duration was 22.5 days per stent with a median total of 176 stent-days per patient. Approximately half had to be removed due to mucus plugging with granulation and migration occurring in a minority of patients. Two cases of major bleeding occurred at stent removal, one leading to cardiac arrest and the other to pneumonectomy. There was no significant difference in complication rates between the different stent products except for a higher (albeit small, 6.5%) fracture rate with the Bonastent.

Holden recently published the largest series of cases of the Bonastent (14). Sixty stents were placed in 50 patients, 90% for malignancy. Most were placed in the bronchus intermedius or trachea, with a mean stent duration was 74 days. Seventy percent of patients had improvement in respiratory symptoms (dyspnea, cough, or stridor) within 30 days. The mean modified Medical Research Council (mMRC) dyspnea scale score decreased over time (lower numbers reflect less dyspnea). The overall complication rate was 54% at a mean follow-up of approximately 4 months, with a higher rate occurring after 30 days. Early complications (<30 days) included mucus plugging, granulation formation, and migration, all occurring in 8% or less of cases. Late complications (≥30 days) were the same but more frequent (25% or less). There were no intraoperative complications.

Ishida and colleagues similarly reported a recent series of patients treated with the Aero stent (15). Forty-two stents were placed in 36 patients; 5 stents were placed for tracheoesophageal fistula with the remainder for malignant airway obstruction. Of the patients that required oxygen prior to stent placement, 78% no longer did, including 5 patients who had been mechanically ventilated. There was also a statistically significant improvement in pulmonary function testing among those for whom this data was available. Stent-related complications occurred in one-third of patients, with 14% experiencing migration and 7% granulation.

Regarding the Ultraflex stent, Chung and colleagues published the largest series to date in 2011 (16). Over a period of approximately 6 years, 149 patients underwent stent placement (72 for benign disease and 77 with malignant). The main indications for those with benign disease were malacia and stenosis due to prior intubation or tuberculosis. The primary reasons for those with malignant disease were airway invasion by lung cancer and tracheoesophageal fistula. Symptoms improved in a higher proportion of patients with benign disease (77%) compared to those with malignant disease (52%). This may be attributed to the additional burden of symptoms and attendant comorbidities in patients with cancer. The overall complication rate was also significantly higher in patients with benign disease (42% *vs.* 21%) but this may be due to the fact that those with benign disease have a longer life expectancy which is also likely reflected in the much higher follow-up time (median, 429 days compared to 57 days). Granulation tissue formation was the most common complication for both groups of patients (19% for benign disease, 10.5% for malignant). The next most common complication was stent fracture for benign disease (16.4%) and stent migration for malignant disease (8.4%).

Also on the Ultraflex stent, Breitenbucher and colleagues published the next largest series in 2008 (17). Sixty-two stents were placed in 60 patients; 82% were covered. Technical success was achieved in all cases. In those for whom pulmonary function tests (PFTs) were available, the mean forced expiratory volume in 1 second (FEV1) significantly improved from 1.45 to 1.78 liters. Overall, complications were noted in approximately one-quarter of patients with mucus plugging (8%) being the most common. Granulation tissue developed in 5%. In most patients, these issues were managed bronchoscopically without requiring stent removal. Tumor restenosis and stent migration occurred in 5% of cases each. There was no stent-related mortality.

Silicone stents

Silicone stents are placed after folding in a loading device and inserting into a metal rod that fits through a rigid telescope. They are typically deployed distal to an area of obstruction and then pulled back into place with long rigid forceps. Unlike metallic stents, customization can be performed at the time of bronchoscopy. For example, they can be trimmed down to a desired length with scissors and side holes can be cut out to allow for aeration of airway branches that might otherwise become unintentionally blocked along the length of the stent.

The first dedicated silicone tracheobronchial stent was described by Dumon in 1990 (18). This was a customized version of the previously used Montgomery T-tube used for

tracheal stenosis and little has needed to change in terms of its design over the years. The Dumon stent (Novatech, La Ciotat, France) has been the standard but other silicone stents exist including the Polyflex (Boston Scientific), the Hood (Hood Laboratories, Pembroke, MA, USA), and the Noppen stents (Reyden Medical Supply, Lennik, Belgium). Silicone stents can be straight, Y-shaped (to stent across a narrowed carina) or hourglass-shaped (with a narrow central portion and wider diameters both ends). They are typically lined with studs that help anchor the stents to the airways but also allow a small space between the airway and the stent, allowing for the continued benefit of mucociliary function. Given their intrinsically-variable shape, the Y and hourglass stents, in particular, can be creatively modified to tailor to the needs of a given obstructed airway (19,20).

In terms of the available data, the largest case series remains the original report by Dumon himself nearly three decades ago (21). One thousand five hundred seventy-four stents were placed in 1,058 patients in four centers in three European countries over 7 years. Most were placed for malignant central airway obstruction. Benign indications included tracheal stenosis and post-surgical stenoses (i.e., post-lung resection or post-transplant). Overall, over half were placed into the trachea and nearly one-quarter in the left mainstem bronchus and slightly less in the right mainstem bronchus. The mean duration of stent placement for cicatricial tracheal stenosis was 1.2 years with the longest duration 6.2 years. For malignant disease, the mean duration was 4 months with the longest duration 4.7 years. Symptomatic outcomes were not described. Complication rates were relatively low with migration occurring in 9.5% of cases, granulation formation in 7.9%, and mucoid obstruction in 3.6%.

The same year as the Dumon study, Cavaliere and colleagues published their experience placing 393 silicone stents in 306 patients as part of a larger series describing therapeutic bronchoscopy for malignant airway obstruction (22). Over one-third were placed in the trachea with an even distribution of stents placed in the right lung, left lung, or a combination. All patients experienced improvement in pulmonary function tests and quality of life (though more specific data were not reported). The median survival of patients with a stent in place was 108 days with a maximum of 1,720 days.

Wood and colleagues described their experience placing 309 stents in 143 patients, 87% of which were silicone (23). Two-thirds of the indications were for malignant disease. Approximately one-quarter had disease primarily involving the trachea, for example, but half had disease involving multiple airways. Notably, 95% of patients experienced significant symptomatic improvement. Regarding complications, 36% had partial obstruction by secretions or granulation and 5% of stents experienced migration.

Dutau *et al.* published a series of 90 Dumon Y-stents placed in 86 patients who had presented with dyspnea, cough, and/or hemoptysis (24). All were placed for consequences of cancer, mostly airway obstruction though some were placed due to airway-esophageal fistula. Only two procedure-related adverse events were reported; one being a week-long cough post-stent and the other being migration of a stent which was subsequently removed without further untoward events. All patients tolerated their stent well and all reported improvement in symptoms, though no formal evaluation tool was utilized to measure this. Average stent duration in situ was 133 days with median time of survival post-stent being 181 days.

Silicone stents have also been used to treat benign airway obstructions. A recent meta-analysis, the first such study of silicone stents for this indication, evaluated 395 patients across 8 studies (25). Silicone stents showed a curative rate over 40%. This was defined as the proportion of patients who were able to have their stents removed without symptomatic restenosis in one year. The stability rate of the stents (proportion of patients who maintained stable stent placement) was similar. As a result, an "effective rate" was over 75%—the sum of the curative and stability rates. In terms of complications, the migration rate was 25% with a granulation rate of 15.7%. No evidence of publication bias was found.

Complications

As mentioned above, airway stents are sometimes met with unintended consequences. The literature has described these thoroughly including the studies mentioned above. In this section, we will put forth studies that specifically examined complications with a more direct and sophisticated analytical approach.

The largest study that specifically looked at complications of stents and therapeutic bronchoscopy came out of the AQuiRE registry (26). Out of over one thousand procedures performed in 947 patients at 15 centers, slightly more than one-third involved stent placement. Among stents placed, 2/3 were metal stents and 1/3 silicone. Overall, among the entire study cohort, only 3.9% of patients experienced a complication with 0.5% resulting in death. Among the eight centers with data on ≥25 cases, complication rates ranged

from 0.9% to 11.7% and the proportion of cases in which a stent was placed ranged from 13% to 69%. On multivariate analysis, risk factors for increased complication rates were urgent and emergent procedures, American Society of Anesthesiologists (ASA) score >3, redo therapeutic bronchoscopy and use of moderate sedation. Stents were not associated with an increased risk of complications. However, also on multivariate analysis, risk factors for increased risk of death within 30 days of the procedure included Zubrod score >1, ASA score >3, any intrinsic or mixed obstruction, and stent placement. Y stents had a higher risk of death [odds ratio (OR) =4.92] than tube stents (OR =1.72). This latter association could be attributed to confounding by the presence of a greater burden of disease in patients requiring a stent or in those for whom all other therapeutic measures had been exhausted with a stent being the final alternative. In all, based on this study, stents are safe but cases should be selected carefully as we have suggested above.

Another instructive study specifically compared patients with and without stents with regard to stent-related infection risk (27). Seventy-two patients with malignant central airway obstruction were evaluated who underwent therapeutic bronchoscopy. Twenty-four of these received one or more stents. Overall, 23 of 72 (32%) developed lower respiratory tract infections (LRTI). A unique and useful aspect of this study was that incidence rates of infection were determined, not just incidence proportions as in most studies (incidence rates are more appropriate because they reflect events per person-time at risk). Also, by comparing stented and non-stented groups, the incremental risk of infection was elucidated. The incidence rate of LRTI in patients with stents was 0.0057 infections per person-day; the corresponding rate in patient without stents was 0.0011 infections per person-day. The resultant incidence rate risk difference of 0.0046 infections per person-day, in turn, translates into a 13% increased risk of LRTI per month. This is equal to one infection for every 8 stents placed. Twenty-six percent of patients with infections died within 2 weeks of stent placement. Indeed, after multivariate analysis, LRTI was associated with mortality. Taken together, this study showed that respiratory infections are increased after stent placement. And, given correlation (though not necessarily causation) with survival, this evidence strongly suggests very judicious use of stents.

Another informative study compared complications of various individual stents (28). Ost and colleagues used time-to-event analysis to evaluate 195 stents in 172 patients: Ultraflex in 60%, Aero in 16% and Dumon silicone stents (either tube or Y-shaped) in 24%. The most common complications were infection, migration, granulation tissue formation, and mucus plugging. Seventy-three patients developed 106 LRTI. The median time to infection was 1 month (range, 0–35 months). Over half of these were hospitalized and nearly one-quarter died within 2 weeks of their infection. On multivariate analysis, only the Aero stent was significantly correlated with infection. This particular outcome was instructive with respect to analytical approaches because the incidence proportion of stent infections was the same across the different stents. However, the incidence rate of stent infections was double for Aero compared to other stents. Regarding migration, this was analyzed only with regard to metal stents and silicone tube stents; because silicone Y stents rarely migrate, these were excluded. Median time to migration was 1.4 months (range, 0–36 months). On multivariate analysis, only silicone tube stents were correlated with this outcome. Regarding granulation tissue, the median time to event was also 1.4 months (range, 0–36 months). Interestingly, silicone stents and LRTI were significantly associated with granulation tissue formation. Mucus plugging occurred in nearly one-quarter of cases with a median time to event of 1.3 months (range, 0–46 months). In the final analysis, a left-sided stent and silicone stents were associated with an increased risk of mucus plugging. There was no statistical association between stent type and hemoptysis, tumor overgrowth, and stent fracture. In terms of overall survival, median follow-up time was 3 months (range, 0–73 months). One hundred forty-six patients of the 172 died. In the final multivariate model, silicone and tracheal stents were associated with decreased mortality but pre-stent radiation therapy and LRTI were associated with increased mortality. These are not necessarily causative relationships, of course, due to the risk of selection bias in this non-randomized study. Silicone stents, for example, will be placed in patients who are fit enough to tolerate rigid bronchoscopy. However, the link between LRTI and survival may indeed be real, as was also suggested by the study by Grosu and coworkers described above.

Overall, stents can certainly be beneficial in select cases but potential complications must be considered in the decision about whether to place one or not in a given case. Even when clearly indicated, however, these unintended consequences must be taken into account and the available data can help determine when/if to perform surveillance bronchoscopy, timing of follow-up, and patient education.

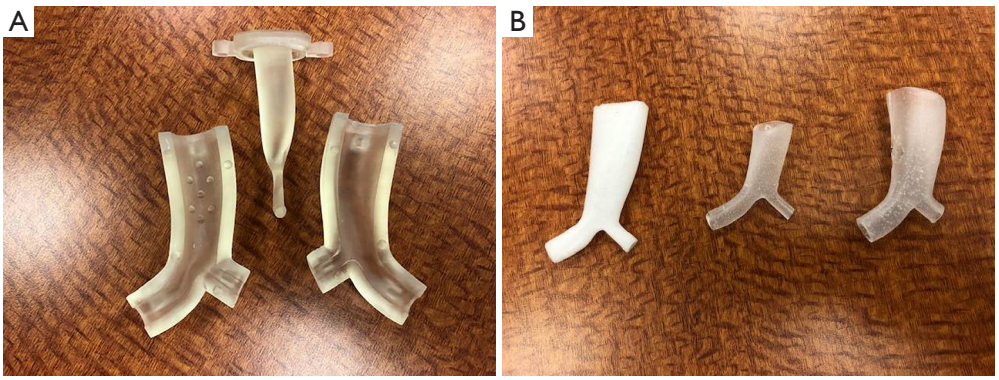


Figure 2 Example of airway stents produced using 3DP technology. A patient's CT scan was imported into 3DP software which was then used to produce a negative mold on a 3D printer (A). Silicone was injected into this mold to produce the final stent product (B). 3DP, three-dimensional printing; CT, computed tomography.

Future directions

Technological advancements regarding airway stents have taken several avenues. Research has been conducted in the effort to develop biodegradable stents that do not require removal but, rather, disintegrate over time. This has the benefit of avoiding a second bronchoscopy for stent removal and theoretically decreases complications since the stents do not remain in place for a prolonged period of time (29). Drug-eluting stents have also been explored, based on the idea that local release of certain agents can treat underlying tumor (cisplatin- or paclitaxel-eluting) or reduce complications (mitomycin-eluting), for example (30-32). These have been reviewed elsewhere (12). In this section, our focus will be on stents produced by three-dimensional (3D) printing as this is a more recent development.

Three-dimensional printing (3DP) is a versatile technology that has made significant inroads into clinical medicine. Applications have been found in various procedural and surgical disciplines, including those treating the nervous, craniofacial, cardiovascular, digestive, genitourinary, and musculoskeletal systems (33). Its introduction into interventional pulmonology is in its early stages but is an attractive investigative idea because stents could be produced that are designed to match a specific patient's anatomy. Obstructed airways can be tortuous and irregular, yet, as described above, typical stents are of a single diameter and rather uniform in their shape. Modifications to attempt to tailor a stent to a given airway are limited: silicone stents can be cut shorter or have a hole cut for ventilation of an airway branch, for example. Y-stents can be ordered with specific angles, widths and lengths but these take weeks to produce and are still of a single diameter in a given limb. 3D printing, theoretically, could allow for a stent to be produced on-site, within hours, and specifically based on a given patient's computed tomography (CT) scan (*Figure 2*).

Initial cases of clinical success with 3D-printed stents have been reported. In France, Guibert and colleagues published the first report of a 3D-printed mold that was made using software that integrated data from a patient's CT scan. Medical grade silicone was poured into this mold to produce a stent that was then placed bronchoscopically to relieve bronchial stenosis in a post-lung transplant patient (7). Immediately after stent placement, the patient experienced durable improvements in dyspnea, quality of life, and objective functional parameters. Soon after this initial report, the same group published a series of 10 such cases of 'anatomically complex airway stenosis', defined as cases in which the stenosis was too complex to allow for a commercially-available stent or in which such a stent had previously failed (34). All stents were implanted without complication via rigid bronchoscopy. At 3 months, there was one case of mucus plugging, two cases of migration, and one case of significant cough; three required removal. Nine of 10 cases were felt to have great congruence between the stent and the airway. Eight of ten demonstrated improvements in dyspnea, quality of life, and pulmonary function testing. Contemporaneously, in the U.S., Gildea *et al.* also used 3D printing to treat the complex airway obstruction of two patients with granulomatosis with polyangiitis (formerly, Wegener's granulomatosis). Both patients improved in a variety of measures as well (35). These stents were initially

used under the FDA's compassionate use program but have since received FDA approval (36). Finally, Schweiger *et al.* also recently reported the use of stents produced in a similar fashion to bring relief to two patients with severe tracheobronchomalacia in Austria (37).

Conclusions

Airway stents are clearly a technology that has been refined over the years. The application of stents must follow a careful cogitation of multiple clinical factors in order to select the proper patient and proper stent. As the field of interventional pulmonology has progressed over time and as research has advanced, we now have the experience and the data to help guide these decisions. Future directions should include the continued development of stents that reduce complications while maintaining their effectiveness.

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Case Report

Asymptomatic lipofibroadenoma in a 17-year-old male: a case report and literature review of a rare entity

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Background: The most common thymic tumours, thymomas, are derived from thymic epithelium and are generally low-grade neoplasm. Frankly malignant tumours, thymic carcinomas are rarer still. Exceedingly rare thymic tumours contain a mesenchymal tissue component such as fibrous connective tissue and/or mature fat. Lipofibroadenoma (LFA) is a very rare mixed epithelial-mesenchymal thymic tumour, included in the category of thymic epithelial tumors. LFA in addition to a mature adipocytic component, contains variable epithelial and mesenchymal tissue components. Owing to the presence of an epithelial component in LFA, this entity, in contrast to thymolipoma, is included in the World Health Organization (WHO) category of thymic epithelial neoplasm. Currently only 12 LFA cases have been described. The 12 previously reported cases all behaved in a benign fashion, although four cases were associated with a conventional type of thymoma. We here present a new, 13th, case of LFA.

Case Description: The LFA was discovered incidentally in a previously healthy 17-year-old male after investigations for suspected pneumonia. On imaging a mass was discovered in the anterior mediastinum which was subsequently surgically removed. The resected tumour was extensively investigated, including the first instance of full molecular analysis of this rare entity and all available literature on LFA was sourced to provide a comprehensive overview. The histology of this LFA was similar to previously described cases. No gene mutations or rearrangements were identified. The patient made an uneventful recovery and after 13 months of follow-up remained well.

Conclusions: An additional, 13th case of LFA is presented. Based on the available literature it appears that LFA may be considered a benign composite thymic tumour, although the combination of an additional conventional thymoma component may warrant closer follow-up.

Keywords: Mediastinum; thymus; thymoma; case report

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Introduction

The vast majority of thymic tumours fall within the category of thymoma. These are primary epithelial neoplasms often admixed with an immature lymphocytic component, thus reflecting to a certain degree organoid thymic differentiation. The World Health Organization (WHO) recognizes two thymic tumours with an adipose component, thymolipoma is considered a primary adipocytic tumour, while lipofibroadenoma (LFA) is included in the category of thymic epithelial tumours but which contains an adipocytic component (1). We here present an incidentally discovered mediastinal tumour in a young male which was resected and subsequently diagnosed as an LFA. This is to the best of our knowledge the thirteenth case of LFA reported in the literature since this entity was first described in 2001 (2) (*Table 1*), and the first case to be analyzed by next-generation sequencing and RNA sequencing (RNAseq). We present the following case in accordance with the CARE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-22-32/rc).

Case presentation

A 17-year-old previously healthy Caucasian male underwent imaging for suspected pneumonia. The magnetic resonance imaging (MRI)-scan (*Figure 1A*) and computed tomography (CT)-scan (*Figure 1B*) showed a hypointense (MRI)/hypodense (CT) tumour with focally more intense (MRI)/denser (CT) areas in the anterior mediastinum, abutting the aortic arch, pulmonary trunk and left ventricle. There was no mediastinal lymphadenopathy and there were no signs of pleural effusion. Based on the imaging investigations, the differential diagnosis included lipomatosis, lipoma/thymolipoma and liposarcoma. As serology did not reveal elevated tumour markers, a germ-cell tumour was considered unlikely. Based on the clinical and radiological findings primary thoracoscopic resection of the tumour and adjacent thymic tissue was performed through the left pleural cavity. After dissection and sealing of the feeding vessel using monopolar diathermy and a bipolar sealing device (Ligsure®, Medtronic, Minneapolis, MN, USA), the specimen was retrieved through an enlarged trocar opening using a thoracoscopic specimen retrieval bag. The recovery was uneventful. The patient was discharged on the third postoperative day.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A thinly encapsulated soft tumour of 12.5×8.0×2.5 cm weighing 153 g was received (*Figure 2A*), which on sectioning mainly consisted of pale yellow fatty tissue with areas of pink-grey fibrous tissue (*Figure 2B*). Fresh tissue, checked by frozen section for the presence of representative constituents, was procured for molecular studies, the specimen was subsequently routinely fixed and processed for histology. A tumour with multiple components was seen in microscopy (*Figure 3A-3D*), areas of mature fat were admixed with pauci-cellular connective tissue with scattered collections of small lymphocytes. The proportion of fatty tissue to collagenous connective tissue varied considerably within the tumour (*Figure 3A*). Throughout these components branching interconnected cords of small epithelial cells were present (*Figure 3B*), occasionally associated with small solid collections of non-atypical spindled cells (*Figure 3C*). Scattered Hassall's corpuscles were present (*Figure 3D*), typically located within lymphoid aggregates. Scattered small calcifications were noted. There was no necrosis, no atypia or nuclear hyperchromasia. Mitotic activity was extremely low. The strands and small foci of spindled cells stained for cytokeratin (pan-cytokeratin AE1-AE3) and p63 (*Figure 4A*,*4B*). The lymphoid aggregates were mainly composed of immature T-cells (CD3/TdT positive) often with small collections of CD20 positive B-cells (*Figure 4C*,*4D*). Molecular analysis was performed by whole exome sequencing (WES) and RNAseq on non-selective tumour tissue samples. For WES total DNA was isolated using the AllPrep DNA/RNA/Protein Mini Kit (Qiagen) according to standard protocol on the QiaCube (Qiagen). DNA-seq libraries were generated with 150 ng DNA using the KAPA HyperPrep Kit in combination with the HyperExome capture kit (Roche) and subsequently sequenced on an NovaSeq 6000 system (2×150 bp) (Illumina). The DNA sequencing data of the tumor and the normal (DNA extracted from blood) were processed as per the GATK 4.0 best practices workflow for variant calling, using a wdl and cromwell based workflow (https://gatk.broadinstitute.org/hc/en-us/sections/360007226651-Best-Practices-Workflows). This included performing quality control with Fastqc (version 0.11.5) to calculate the number of sequencing reads and

Table 1 Published cases of LFA

No.	Authors	Year	Gender, age (years)	Symptoms, duration	Size	Associations	Follow-up [months]
1	Kuo and Shih (2)	2001	Male, 62	Dyspnea, dizziness, PRCA	ND	B1 thymoma, PRCA	No recurrence of tumor [80], PRCA relapse 2× after removal of tumor
2	Onuki *et al*. (3)	2009	Male, 32	Incidental finding in work-up for pneumonia, 6 months	3 cm	–	ND
3	Wang *et al*. (4)	2009	Male, 56	Cough, expectoration, 2 weeks	4.5 cm	B1 thymoma	NED [24]*
4	Aydin *et al*. (5)	2012	Female, 23	Chest pain, dyspnea, 6 months	21 cm, 2,180 g	B1 thymoma (proposed composite B1 thymoma and lipofibroadeoma)	NED [12]
5	Qu *et al*. (6)	2013	Male, 21	Asymptomatic, incidental finding	10 cm	–	NED [46]
6	Makdisi *et al*. (7)	2015	Male, 20	Acute onset of fever and cough	23 cm, 670 g	–	NED [6]
7	Hui *et al*. (8)	2018	Male, 29	Cough, expectoration 6 months	6.5 cm	B1 thymoma	ND
8	Hamada *et al*. (9), Kurebayashi *et al*. (10)	2018, 2021	Female, 55	Asymptomatic, incidental finding on PET-CT	4.5 cm	Thymic hyperplasia	NED [12]
9	Kojima *et al*. (11)	2018	Male, 29	Asymptomatic	6 cm	–	ND
10	Hakiri *et al*. (12)	2021	Male, 28	Asymptomatic, incidental finding	9 cm	–	NED [6]
11	Matyjek *et al*. (13)	2021	Female, 35	Fatigue, cough	26 cm	ANCA-associated vasculitis with renal involvement	NED [12]; progressive renal deterioration
12	Bolca *et al*. (14)	2021	Female, 64	Progressive dyspnea	16 cm, 2,800 g	–	NED [48]
13	Current report	2022	Male, 17	Incidental finding in work-up for pneumonia	12.5 cm, 153 g	–	NED [13]

*, follow-up estimated from publication date. LFA, lipofibroadenoma; PRCA, pure red cell aplasia; ND, no data; NED, no evidence of disease; PET, positron emission tomography; CT, computed tomography; ANCA, anti neutrophil cytoplasmic antibody.

the insert size Picard (version 2.20.1) for DNA metrics output and MarkDuplicates (15). mRNA sequencing was performed as previously described (16). In brief, total RNA was isolated using the AllPrep DNA/RNA/Protein Mini Kit (Qiagen) according to standard protocol on the QiaCube (Qiagen). RNA-seq libraries were generated with 300 ng RNA using the KAPA RNA HyperPrep Kit with RiboErase (Roche) and subsequently sequenced on an NovaSeq 6000 system (2×150 bp) (Illumina). The RNA-seq data were processed as per the GATK 4.0 best practices workflow for variant calling, using a wdl and cromwell based workflow (https://gatk.broadinstitute.org/hc/en-us/sections/360007226651-Best-Practices-Workflows). This included performing quality control with Fastqc (version 0.11.5) to calculate the number of sequencing reads and the insert size Picard (version 2.20.1) for RNA metrics output and MarkDuplicates (15). The raw sequencing reads were aligned using STAR (version 2.7.0f) to GRCh38 and gencode version 29 (16). Finally, expression counts were determined at gene level using Subread Counts (17). Fusion

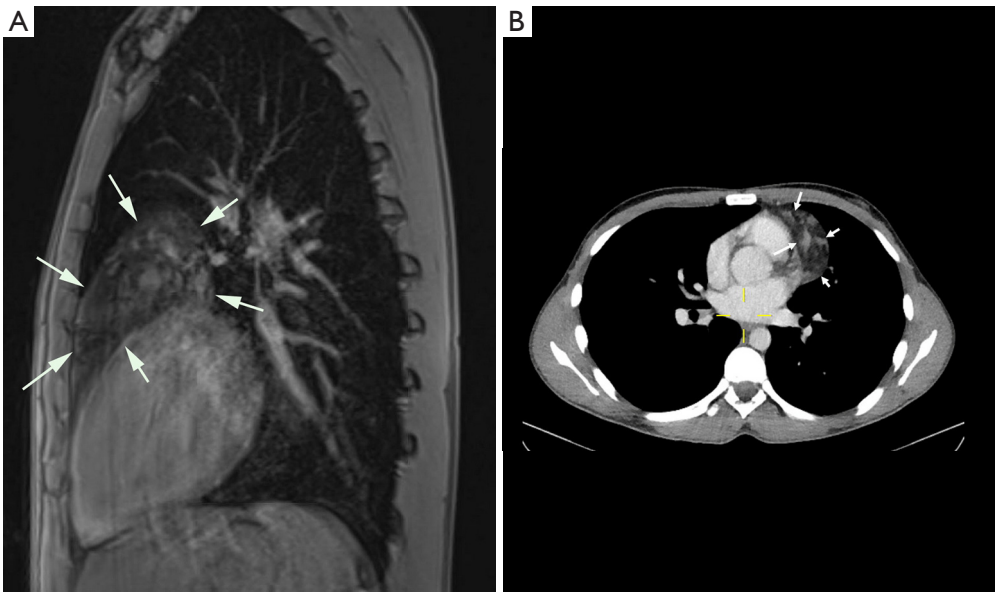

Figure 1 MRI and CT-scan. (A) Post-contrast T1 vibe (volumetric interpolated breath-hold examination) fat saturated sagittal MR-image, depicting a supra-cardial fatty mass (indicated by arrows). (B) Contrast-enhanced transverse CT-image showing the left para-cardial located low density mass (indicated by arrows). MRI, magnetic resonance imaging; CT, computed tomography; MR, magnetic resonance.

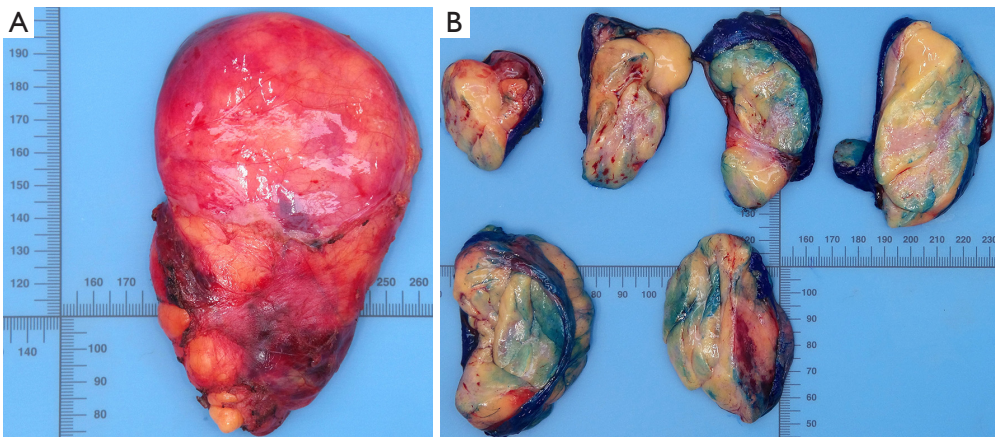

Figure 2 Gross image of resected tumour. (A) Thinly encapsulated 12.5 cm excised tumour. (B) On sectioning a predominantly fatty specimen is seen with focally grey fibrous areas.

gene detection was performed using STARfusion.

No relevant somatic mutations or copy number variation (CNV) were detected through WES, no gene rearrangements were identified by RNAseq. Based on the findings a diagnosis of thymic LFA was made. Following surgery the patient made a good recovery and at 9 months follow-up there was no evidence of disease.

Discussion

The vast majority of thymic neoplasms are derived from thymic epithelium. Of these most are thymomas and behave as low-grade neoplasms, of which different histological subtypes are recognized in the WHO classification (1). A lymphocytic component is present in most subtypes of

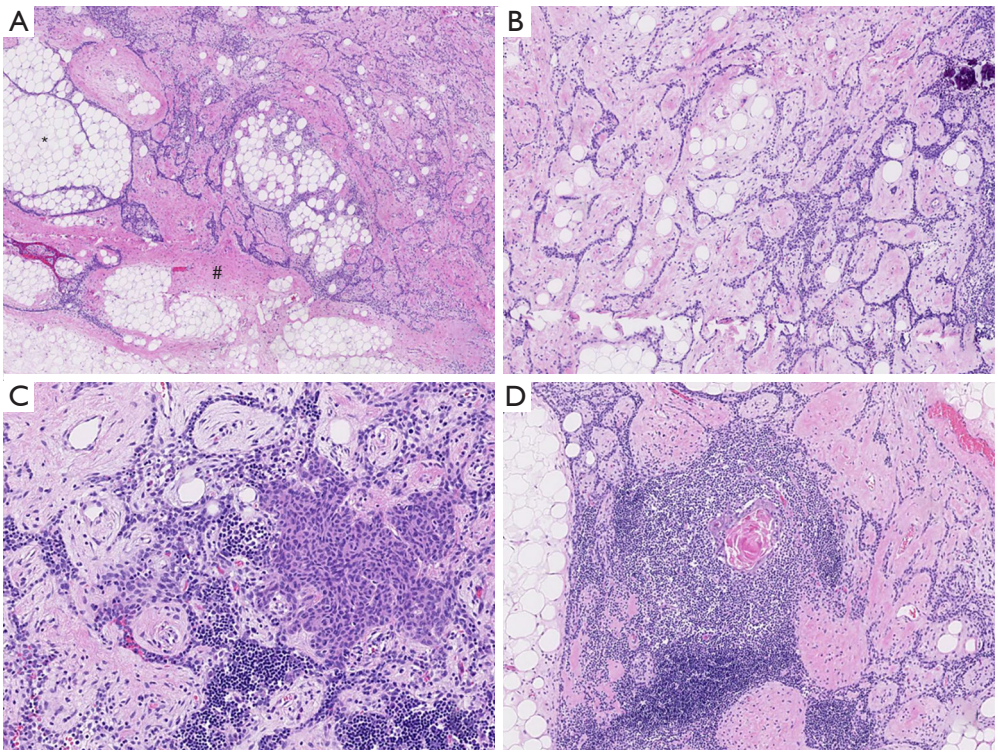

Figure 3 Histology. (A) Fibro-fatty tissue with ramifying cords of epithelial cells. Mature fatty tissue, present in several areas in this slide (a single area indicated by *). Pink fibrous collagenous tissue is indicated (#). Darker branching strands of epithelial cells ramify through both fibrous and fatty tissue. (B) Scattered small calcifications were present, again note the slender strands of epithelial cells. (C) Discrete collections of spindled epithelial cells, comparable to those of a spindle cell thymoma. (D) Lymphoid component with a Hassall's corpuscle. HE stained sections (A,B: low power view; C,D: medium power view). HE, hematoxylin-eosin.

thymoma reflecting differentiation along the lines of the normal thymus. However, mesenchymal tissue does form part of the thymoma spectrum and as such is exceedingly rare in a primary thymic tumour, the only exception being somatic mesenchymal tissue elements in thymic germ-cell tumours. Only two primary non germ-cell thymic tumours with a mesenchymal component have been conclusively described, thymolipoma and LFA. It has been suggested that a third malignant mesenchymal (adipocytic) tumour in the mediastinum may originate in the thymus (thymoliposarcoma) (18).

Thymolipoma is a primary thymic adipocytic neoplasm consisting of mature fat which may reach a large size before producing symptoms. While scattered islands of otherwise normal thymic tissue are commonly present within the fatty tissue of thymolipoma, these are not thought to be part of the neoplasm but rather entrapped normal thymic tissue. Recently a case was described with an extensive, partly organoid, thymic epithelial component combined with areas in keeping with thymolipoma, thus blurring the border between thymoma and thymolipoma (19). Support for the neoplastic nature of thymolipoma is the identification of a *HMGA-2* mutation (20). Variants of thymolipoma have been described with an excess of connective tissue, thymofibrolipoma, and with a conspicuous vascular component, thymohemangiolipoma (21-24).

In contrast to thymolipoma, LFA contains a characteristic epithelial component in addition to the lipomatous component. Therefore, in the current WHO classification thymolipoma is considered a thymic mesenchymal tumour while LFA is classified as a thymic epithelial tumour (1).

In all documented cases the epithelial component of LFA consists of small bland cells with sparse cytoplasm arranged in interconnected strands and cords ramifying through the connective tissue and fat. The typical branching epithelial strands, somewhat reminiscent of mammary fibroadenoma, prompted the designation LFA in 2001 (2). The epithelial strands are intimately associated with both

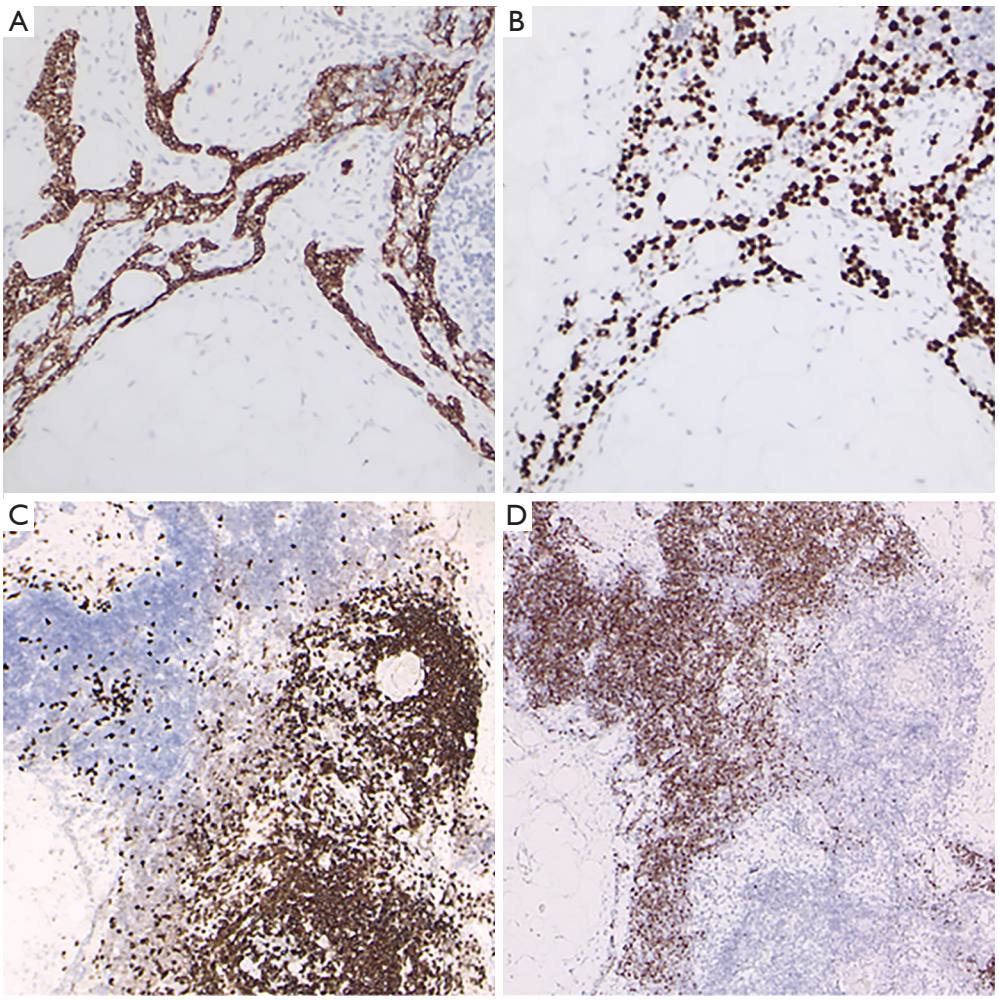

Figure 4 Immunohistochemistry. The epithelial strands are highlighted in the AE1/AE3 cytokeratin (A) and p63 (B) stains (medium power views). The lymphoid component shows a mixed B-cell (CD20 positive) population (C) combined with an immature (TdT positive) T-cell population (D) (medium power views).

the lipomatous tissue and pauci-cellular connective tissue. Features suggesting malignancy such as atypia, conspicuous proliferative activity and necrosis have not been described in LFA. The lipomatous component consists of mature fat cells devoid of lipoblasts. Pronounced calcifications were described in a single report, prompting the consideration of a germ-cell tumour (12). Small calcifications were previous described in LFA (11), and were also present in our case. In the case we present here small foci with increased cellularity were present, composed of more spindled cells, reminiscent of those seen in type A/AB thymoma. The lymphocytic component in LFA is generally poorly developed, immature TdT positive lymphocytes may be present (10-12), as in the case presented here, or may be absent (4,7-9).

Whether thymofibrolipoma and LFA are separate tumour entities or form a spectrum of composite lipomatous thymic tumours is not clear. Makdisi *et al.* group thymofibrolipoma together with LFA (7). Indeed, the images in the article by Moran, Zeren & Koss show histological overlap with LFA with strands of cells in fibrous tissue, suggestive of a thymofibrolipoma-LFA tumour continuum (22). However, this feature is not clearly seen in the thymofibrolipoma case presented by Kang *et al.* (21).

Patients with LFA are usually young (range, 17–64 years, median age 29 years), with a male predominance (4/9 female/male ratio) (2-12,14). Most LFA cases described to date were discovered incidentally by investigations performed for unrelated symptoms. If symptoms were

present, these were non-specific consisting of cough or dyspnea. A single case of red cell aplasia has been reported, but in this case the LFA was associated with a B1 thymoma, which may well account for the para-neoplastic pure red cell aplasia (2).

Interestingly, in four of the hitherto described cases, the LFA was associated with a B1 thymoma, which given the rarity of both thymoma and LFA is suggestive of a pathogenetic relationship (details of reported cases in *Table 1*) (2,4,5,8). The follow-up of all reported cases after surgical removal of the LFA is favorable, no recurrences have been reported and patients made a good recovery. While the patient described in the report by Matyjek and co-workers made an initial good recovery from the operative procedure to remove a large LFA, she did suffer progressive anti neutrophil cytoplasmic antibody (ANCA)-vasculitis associated renal failure (13). Although it was suggested that the vasculitis may have been associated with the LFA given the co-occurrence of two rare diseases, this may be contested as the ANCA-associated vasculitis progressed after removal of the LFA. Current evidence suggests that LFA behaves in a benign fashion and only limited follow-up after removal is indicated. In those cases where as associated sub-type is present, as in the three reported cases associated with B1 thymoma it would be prudent to base the follow-up on the associated thymoma.

The nature of LFA is uncertain. The mixed composition of LFA could be taken as indicative for a hamartomatous origin rather than a true neoplasm. However, the circumscription, encapsulation and occasional large size are more in keeping with a neoplastic process. In the case presented here we did not identify genetic aberrations, specifically no *HMGA-2* mutation was found, as described recently in thymolipoma, nor were CNVs documented. In a single recently described LFA case no fusion transcripts were detected (13), taken together with our case, there are currently no features which support a neoplastic process.

Conclusions

In conclusion, we report the 13th case of a rare mixed epithelial-mesenchymal tumour, LFA. The reported case bears many similarities to reported cases and adds to the awareness of this rare entity.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Editorial Commentary

Postoperative complications of mediastinal cyst resection and their management

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The incidence of complications after resection of mediastinal cysts is not well described in the literature. The incidence of complications after resection of mediastinal cysts reported in few case reports and small case series vary between 2–7% (1-4). Most complications that occur after resection of mediastinal cysts are similar to those that occur after any thoracic procedure (2,3) (*Table 1*,*2*). Sound knowledge of the possible postoperative complications allow the surgical team to anticipate postoperative complications and thus reduce this morbidity.

Postoperative respiratory complications

Postoperative pulmonary complications are reported after resection of mediastinal cysts (4). Following any thoracic surgery, respiratory function is impaired to varying degrees depending on the approach used. With open surgery having much higher incidence of respiratory complications than minimally invasive approaches (4). Respiratory complications after mediastinal cyst resection range from atelectasis, pleural effusion, to pneumonia (3,4,9). Atelectasis is a common postoperative pulmonary complication. If not managed aggressively, atelectasis can develop into pneumonia.

The impact of these respiratory complications is not only clinical but also economical given that they result in longer hospital stay (7,10,11). Risk factors for developing postoperative pulmonary complications following thoracic surgery include age, pulmonary function tests, cardiovascular co morbidity, current smoking and chronic obstructive pulmonary disease (10-12).

Respiratory complications after mediastinal cyst resection can be diminished by optimizing the patients preoperatively, choosing minimally invasive approaches, and focusing on the basics of postoperative care, such as pulmonary physiotherapy, fluid management, and pain control (3,4).

Postoperative bleeding

Another complication, which may happen early after resection of mediastinal cyst is postoperative bleeding (3). Bleeding immediately postoperative can be due to technical complication or coagulopathy. Generally postoperative bleeding is caused by technical complications. Postoperative bleeding usually presents with high chest tube output or hemodynamic instability. As soon as bleeding is suspected, coagulation blood tests should be performed, and coagulopathy rectified accordingly. Given that most postoperative bleeding is caused by technical complications, the surgeon should have a very low threshold to take the patient back to the operating room for re-exploration. To prevent postoperative bleeding whenever a vascularized cyst is anticipated, embolization of afferent vessels has been performed in order to reduce surgical bleeding (12).

Infections

Infectious complications after mediastinal cyst resection are not reported frequently in the literature, since the chest wall has multiple blood supplies (12). The reported incidence

Table 1 Complications of mediastinal cyst resections and their management

Complications	Characteristics	Prevention/management
Postoperative respiratory complications	Atelectasis, pleural effusion, and pneumonia	Optimize patient preoperatively
	Respiratory function is impaired to varying degrees depending on the approach used	Choose minimally invasive approach when possible
		Focus on postoperative care (fluid management, pain management, pulmonary hygiene and chest physiotherapy)
Postoperative bleeding	Postoperative bleeding can be due to surgical bleeding or coagulopathy	Preoperative embolization of afferent vessels → to reduce surgical bleeding complications when a vascularized cyst is anticipated
	Most common due to technical complications	Correct coagulopathy
	Presents with high chest tube output or hemodynamic instability	Low threshold to take back a patient for re-exploration and control of bleeding
Infection	Rare complication since the chest wall has an excellent blood supply and these procedures are considered clean procedures	Preoperative antibiotics prophylaxis
	Incidence in the literature varies from 5% to 24.4%	Postoperative infections should be treated with antibiotics
Cardiac complications	Very common complication after any thoracic surgery	Medical management
	The most common arrhythmia that happens after thoracic surgery is supraventricular tachycardia	
Reperfusion lung injury	Happens after resection of cysts that are compressing the pulmonary artery	Prevent this complication by gradually aspirating cyst before extraction
Chylothorax	Reported as the most common postoperative complication after resection of mediastinal cysts	First line of management of chylothorax → conservative treatment (medium chain triglycerides diet)
	Chylothorax is caused by incomplete ligation of lymphatic channels or direct injury to the thoracic duct during resection of mediastinal cysts	If the chyle leak does not resolve after the use of medium chain triglycerides → total parenteral nutrition should be considered to reduce the chyle flow
		If chylothorax does not respond to the conservative management → reoperation is required
Chylopericardium	Rare complication that happens after mediastinal cyst resection	Management and prevention strategies for chylopericardium are the same as the ones discussed for chylothorax
	Reported to occur when chyle leaks into the pericardial cavity instead of the thoracic cavity because of a previous pleurodesis	
Injuries to structures surrounding mediastinal cyst	Injuries can occur to surrounding structures (esophagus, phrenic nerve, recurrent laryngeal nerve, azygos vein, aorta, and bronchus)	Detailed anatomic knowledge and meticulous dissection helps to prevent these complications
	Injuries to surrounding structures are more common when there are adhesions or in redo surgeries.	
	Injuries to the phrenic nerve → occur when resecting an anterior mediastinal cyst	
	Injury to the vagus nerve	
	Injury to the recurrent laryngeal nerve → occur when resecting an anterior mediastinal cyst	

Table 1 (*continued*)

Table 1 (*continued*)

Complications	Characteristics	Prevention/management
Recurrence	Potential long-term complication	Recurrence is avoided by complete removal of the cyst
	Most recurrence is due to incomplete surgical resection	If a recurrence occurs → it is advised to resect the cyst before the appearance of symptoms
	Recurrence is also more likely to happen when attempting resection of infected cysts, mediastinal lymphangiomas, and multi-loculated cysts and bronchogenic cysts	

The arrows indicate next step.

Table 2 Complications reported after resection of different types of mediastinal cysts

Mediastinal compartments	Cyst types	Locations	Specific reported complications
Anterior mediastinum	Thymic cyst	Anterior mediastinum	Phrenic nerve paralysis and chylothorax (5,6)
Middle mediastinum	Bronchogenic cysts	One third in middle mediastinum (4,7)	Recurrence if cyst not completely excised (3,4,7)
		Two thirds extend to the limits of the posterior portion of the mediastinum (4,7)	
	Esophageal cysts	Most commonly found embedded in the wall of the lower half of the esophagus (8)	Tracheal and esophageal injuries, pseudodiverticulum development, and vagus nerve injury or paralysis (8)
	Pericardial cysts	50–70% located in cardiophrenic angle (9)	Phrenic nerve injury (9,10)
		30–50% in the visceral compartment (9)	
Posterior mediastinum	Neurenteric cyst	Posterior mediastinum	Chylothorax (9,10)

of infectious complications varies from 5% to 24.4% (3,4). These procedures are considered clean procedures, except for resection of some foregut cysts that may have secondary infection (3,4). Antibiotic prophylaxis should be administered preoperatively, and postoperative infections should be treated with antibiotics and drainage if required (4).

Cardiac complications

Arrhythmias are reported after any thoracic surgery (3,4,7,10,13). Risk factors for arrhythmias include: cardiovascular co-morbidities, postural change, anesthetic agents, extensive dissection, intraoperative bleeding, previous thoracic irradiation and age (2,3,14).

Reperfusion lung injury

Reperfusion lung injury can happen after resection of cysts that are compressing the pulmonary artery (7,14). To avoid such a complication, gradual aspiration of the cystic fluid before extraction of the cyst is advised (14).

Chylothorax

Chylothorax is reported as a common postoperative complication after resection of mediastinal cysts (9,10,13). The incidence of chylothorax after mediastinal cyst resection varies in the literature (9,10,13,14). Etiologies of chylothorax include resection of mediastinal cyst with incomplete ligation of lymphatic channels or direct injury to the thoracic duct at the time of the resection (9). Chylothorax causes loss of proteins, vitamins, and fat which leads to metabolic and nutritional deficiencies. A prompt diagnosis is essential to prevent chylothorax complications. The first line of management of chylothorax is conservative treatment (13,14). Conservative treatment involves replacing the lost proteins and fat. In addition to, draining large chylothoraces to ensure that the lung expands completely (9,10). The administration of medium chain triglycerides is recommended for these patients,

because they are absorbed directly into the portal system. If the chyle leak persists after the administration of medium chain triglycerides then total parenteral nutrition should be started to reduce the chyle flow.

If chylothorax does not respond to the conservative management, then, reoperation is required (9,10,13,14). If the thoracic duct is identified during the operation then ligatures or clips can be used to ligate the thoracic duct (9,10). If the thoracic duct is not identified, then mass ligature of the tissues between the aorta and azygos vein at the level of the diaphragmatic hiatus resolves the chylothorax (9,13). In symptomatic high risk patients, embolization of the thoracic duct or endoscopic aspiration with the injection of a sclerosing agent should be considered (9).

To prevent chylothorax after resecting a mediastinal cyst, Mortman et al. advised to ligate both the afferent and efferent limbs of the thoracic duct feeding the cyst (9). Yet, despite ligating the afferent and efferent limbs of the thoracic duct, Mortman et al. reported a chylothorax (9).

Chylopericardium

Chylopericardium can happen after mediastinal cyst resection (9,10). Chylopericardium occurs when chylous fluid accumulates in the pericardial cavity. Chylopericardium is reported to occur when chyle leaks into the pericardial cavity instead of the thoracic cavity because of a previous pleurodesis (10). The management and prevention strategies for chylopericardium are the same as the ones discussed for chylothorax (9,10,13). It is recommended that the pedicles should be ligated in mediastinal cyst resections (10). Additionally, careful intraoperative assessment may help localize any point of chyle leakage (10). Conservative management, including low-fat diet, is the first preference in the initial management of postoperative chylopericardium (9,10,13,14). If no response to conservative treatment after >2 weeks then surgical repair should be considered (10).

Injuries to surrounding structures

While resecting mediastinal cysts, nearby structures are at risk of injury. Injuries can happen to the esophagus, phrenic nerve, recurrent laryngeal nerve, azygos vein, aorta, and bronchus (2,3,7,9-11,14).

Injuries to the phrenic nerve

Injury to the phrenic nerve can occur when resecting an anterior mediastinal cyst. It is more common for injuries to occur in redo surgeries and when there are adhesions (11,13-15). Injuries to the phrenic nerve may result in temporary or permanent diaphragmatic paralysis. This can cause the patient to have shortness of breath on exertion, atelectasis, and decreased exercise tolerance. If the patient is on a ventilator postoperatively, then it might be difficult to wean the patient off the ventilator. Usually, it is initially suspected on a chest X-ray (CXR) that shows elevation of the affected hemi diaphragm. Diagnosis can be confirmed with ultrasound or fluoroscopy. If the patient is symptomatic, or cannot be weaned from the ventilator, then, diaphragmatic plication is the best method for management (11,15).

Injury to the vagus nerve

Injury to a vagus nerve can also occur during resection of mediastinal cysts (10,13,14). Usually, one vagus nerve is injured during resection of mediastinal cysts, and the other intact vagus nerve provides parasympathetic input to the gastrointestinal tract.

Injury to the recurrent laryngeal nerve

Injury to the recurrent laryngeal nerve can occur when resecting an anterior mediastinal cyst (7,13,14). Injuries to the recurrent laryngeal nerve usually presents with a weak, hoarse, and whispery voice postoperatively. Patients would usually complain off their voice getting weaker as the day progresses. Such injuries may cause aspiration due to inability to cough effectively. Laryngoscopy is used to confirm the diagnosis. Treatment depends on whether the injury is temporary or permanent.

Other complications that can happen after mediastinal cyst resection include pulmonary embolism, deep venous thrombosis, renal failure, and strokes (2-4,9,10,13). These complications should be recognized early and aggressively managed.

Recurrence

Recurrence of the mediastinal cyst is a possible long-term complication (3,4,7). It can happen in some cases even as far as 20 years after resection (3,4,7,13). Many case reports attribute their recurrence to incomplete surgical resection (3,4,7). Incomplete resection can happen if the entire mucosal lining of the mediastinal cyst is not completely

resected. Cases in which this is more likely to happen are those in which a part of the cyst is adherent to critical mediastinal structures. It is also more likely to happen when attempting resection of infected cysts, mediastinal lymphangiomas, and multi-loculated cysts (11,15,16). Incomplete cyst resection can also occur in patients with bronchogenic cysts because of severe adhesions between the cyst and the tracheal wall and pulmonary artery (1). In addition, incomplete resection is more likely to happen when video-assisted thoracic surgery (VATS) approach is used because of limited visibility and mobility during the operation, while standard open thoracotomy and the robotic approach do not have this issue.

Recurrence of mediastinal cysts can sometimes precipitate potentially serious vascular and pulmonary complications (3). These should be avoided by complete removal of the cyst. Removal of cyst margins is still, however, controversial (2). If a recurrence occurs, it is advised to resect the cyst before the appearance of symptoms (13).

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