Review Article

Esophageal duplication cysts: a clinical practice review

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Abstract: Esophageal duplication represents one of the most common types of bronchopulmonary foregut malformations. These rare congenital anomalies occur secondary to embryological aberrations between the 4th and 8th weeks of gestation. In order to be classified as an esophageal cyst a mediastinal cyst must have a close proximity with the esophagus, be lined by alimentary (squamous epithelium) or tracheobronchial mucosa and covered by two smooth muscle layers. These rare anomalies are often asymptomatic during adulthood. However, they can cause symptoms in early childhood, generally during the first 2 years of life. Variations in location, size, presence or absence of heterotopic mucosa, will dictate the clinical presentation. Dysphagia, food impaction, persistent cough and chest pain are common clinical presentations. Imaging studies including esophagram, computed tomography (CT) and magnetic resonance imaging (MRI) can provide key findings to reach the diagnosis. Nonetheless, endoscopic evaluation, particularly endoscopic ultrasound (EUS) is the most valuable tool to determine whether this lesion is cystic versus solid and or if there are abnormal mucosal findings. Needle biopsies are controversial but can help with drainage and to rule out malignant transformation. Therapeutic options include endoluminal drainage. However, more definitive therapies include surgical excision. Open and minimally invasive (laparoscopic and thoracoscopic) techniques have been demonstrated to be safe and effective at completely removing these lesions. Recently, robotic-assisted resections have gained more attention with case reports and series reporting excellent outcomes.

Keywords: Esophagus; congenital; duplication cyst; thoracic surgery

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Introduction

Esophageal duplication cysts are rare congenital anomalies that constitute between 0.5% and 2.5% of all esophageal masses (1). It is estimated that the incidence of esophageal duplication cysts is one in 8,200; they are twice as likely to occur in males when compared to females (2,3). The exact etiology of alimentary tract duplications is not well understood. However, it is thought to occur between the 4th and 8th weeks of development as a result of failure of intrauterine vacuolization of the esophagus (1). The duplication cysts lay within the esophageal wall, falling under the category of intramural lesions and need to be distinguished from esophageal malignancies, leiomyomas, lipomas, and gastrointestinal stromal tumors (GISTs). Esophageal duplications cyst can be lined by alimentary (squamous epithelium) or tracheobronchial mucosa regardless of where they are located. They have an envelope of smooth muscle and share a common wall with the esophagus (2,4). Up to one-third of esophageal duplication cysts contain heterotopic gastric mucosa; heterotopic pancreatic mucosa and mucosa consistent with Peyer's patches have also been described (5,6). Approximately 80%

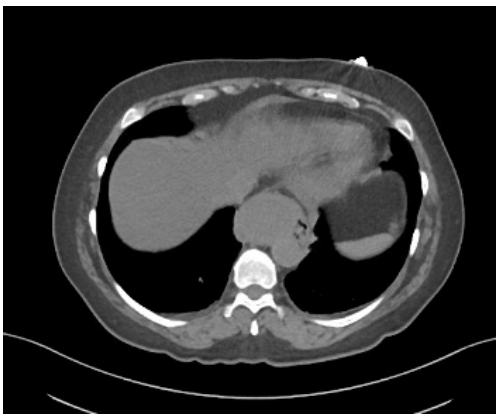

Figure 1 CT axial view demonstrated complex duplication cyst of the esophagus with extrinsic compression of esophageal lumen. CT, computed tomography.

of esophageal duplication cysts do not communicate with the esophageal lumen, whereas tubular duplications do have a direct communication with the lumen.

Clinical presentation

Patients with esophageal duplication cysts often remain asymptomatic, however those that become symptomatic usually present during childhood (1). During adulthood most esophageal duplication cysts are found incidentally while patients are undergoing work-up for unrelated conditions. Esophageal duplication cysts are most likely to be found in the lower third of the esophagus and the remaining are found in the upper/middle third of the esophagus (7). Clinical presentation varies depending on the location of the cyst. Those located within the upper esophagus are associated with respiratory manifestations including, dyspnea, stridor, respiratory distress, mass effect, retrosternal pain and cough. Whereas those located in the lower third of the esophagus are mainly associated with dysphagia, esophageal stenosis, food impaction and emesis. Although rare, hematemesis has been reported in the presence of heterotopic gastric mucosa. Additionally, cardiac arrhythmias, bleeding and rupture with complicated mediastinitis have also been reported in the literature (8). Due to the clockwise rotation of the stomach during embryogenesis, esophageal duplication cysts most commonly lay on the right lateral aspect of the esophagus (2).

Diagnosis

Benign esophageal lesions are often times asymptomatic and incidentally encountered during endoscopic or radiologic evaluation of the esophagus. Nevertheless, they pose challenges in establishing an accurate diagnosis and management plan. In the work-up of an esophageal duplication cyst, plain radiographs may demonstrate a well-defined soft tissue density in close association with the esophagus or widening of the mediastinum. A barium esophagram is an excellent study to delineate the anatomy of the esophagus, assess mucosal irregularities and visualize the location of the duplication cyst in relationship to surrounding organs. The esophagram can show an extrinsic versus and intramural compression on the wall of esophagus. Furthermore, intraluminal communication can also be recognized during this study. We routinely order an esophagram for pre-operative planning and post operatively to have a new baseline of the neo-anatomy post excision.

Computed tomography (CT), preferably, with intravenous contrast assists to delineate thick-walled cystic structures that can have complex versus simple fluid within. Generally, the cysts have smooth contour and low attenuation, with Hounsfield units ranging from 8 to 12 corresponding to water density. However, cysts can be filled with proteinaceous complex material, suffer spontaneous rupture or post instrumentation hemorrhage leading to images with hyper attenuating characteristics and elevated Hounsfield units closer to blood density (*Figure 1*). With the usage of oral contrast, filling defects are sometimes seen, but since duplication cysts are generally submucosal lesions, the lining appears smooth and with normal characteristics. While the differentiation between bronchogenic cysts and esophageal duplications cysts ca be challenging, a close relationship with the esophagus, lack of cartilaginous components and the presence of a double smooth muscle layer favors the diagnosis of an esophageal duplication cyst over bronchogenic cyst.

Further imaging modalities include magnetic resonance imaging (MRI) that shows the cystic nature of the mass as well as high intensity when imaged with T2-weighted sequences, regardless of the nature of the cyst contents. In the pediatric population, radionuclide scanning with Technetium 99m sodium pertechnetate assists with the localization of ectopic gastric mucosa, as the technetium is up taken by the gastric mucosa and this can be visualized

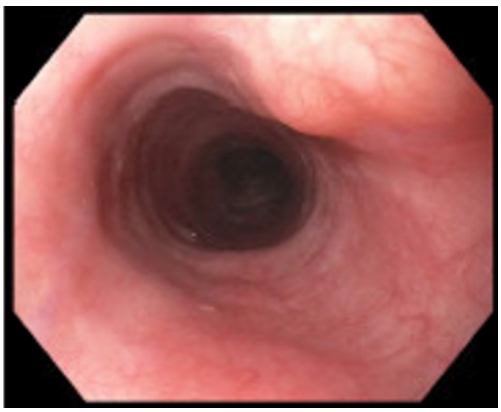

Figure 2 Esophagoscopy demonstrating extrinsic compression of the esophageal wall at 35 cm from the incisors with normal appearing mucosa.

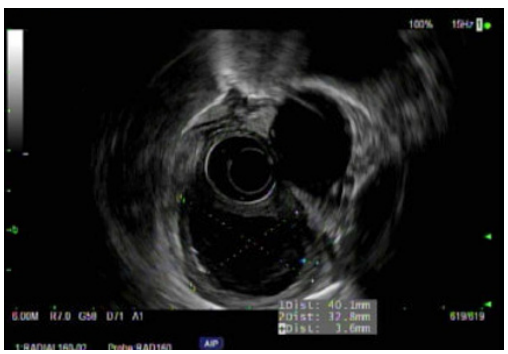

Figure 3 EUS with anechoic cystic lesion in direct contact with the esophagus and thickened wall consistent with esophageal duplication cyst. EUS, endoscopic ultrasound.

with nuclear scans (9).

Positron emission tomography (PET) CT should only be ordered if malignant transformation of the duplication cyst has been confirmed with tissue biopsy. In this case, a PET scan will allow further investigation regarding invasion and whether there is spread to mediastinal or distant structures.

On esophagogastroscopy, duplication cysts appear as submucosal lesions with normal appearing esophageal mucosa (*Figure 2*), differential diagnosis include leiomyoma, GISTs and lipomas (10). Endoscopic ultrasound (EUS) demonstrates homogenous hypoechoic periesophageal multi-layered wall mass. Margins are generally smooth and the muscularis propria of the esophagus is in direct contact with the cyst wall (11).

The role of EUS-guided fine needle aspiration (EUS-FNA) in the diagnosis of esophageal duplication cysts is controversial. Studies have shown an infection rate as high as 14% when EUS-FNA is performed (12,13). EUS-FNA should be reserved for lesions of indeterminate appearance, lesions concerning for malignancy and lesions that appear atypical (*Figure 3*).

Once diagnosis has been confirmed, an open discussion with patients regarding risks and benefits of surgical excision is recommended for a shared decision making approach. Surgery can be considered for both asymptomatic and symptomatic patients given the risk of future complications or malignant transformation (14,15). These lesions do not regress spontaneously and identification of the entire tract is key to ensure adequate resection. The surgical approach can be open, through a laparotomy or thoracotomy, or via minimally-invasive techniques dependent on the skill set of the surgeon. Minimally-invasive approaches have been demonstrated to be safe, feasible and with excellent outcomes (16,17). Given that the majority of esophageal duplication cysts are localized to the distal esophagus, herein we describe our trans-abdominal approach for surgical excision using the robotic platform. Cervical and thoracoscopic approaches are better reserved for upper and mid-esophageal lesions.

Surgical approach

The patient is placed in the operating table with a footboard and all the pressure points adequately padded. Our patients receive preoperative antibiotics with a first generation cephalosporin and deep vein thrombosis prophylaxis routinely. A foley catheter and arterial line are also placed for continuous monitoring of the urine output and blood pressure. We utilize four robotic ports, the first (camera port) is placed 2 cm above and towards the left from the umbilicus. The second port is place in the left hemi abdomen, at the peritoneal reflexion, a third robotic port is placed in between the two prior ones and the fourth robotic arm is placed in the right upper quadrant. An assistant (12 mm) port goes in the left lower quadrant. Finally, a subxiphoid 5 mm port for the liver retractor (picture). the robot is routinely armed with the cadiere forceps (arm 1), camera (arm 2), vessel sealer (arm 3) and the curve bipolar and double fenestrated (interchange in arm 4) (*Figure 4*).

We start by dissecting at the phrenoesophageal membrane to enter the diaphanous plane of dissection. We

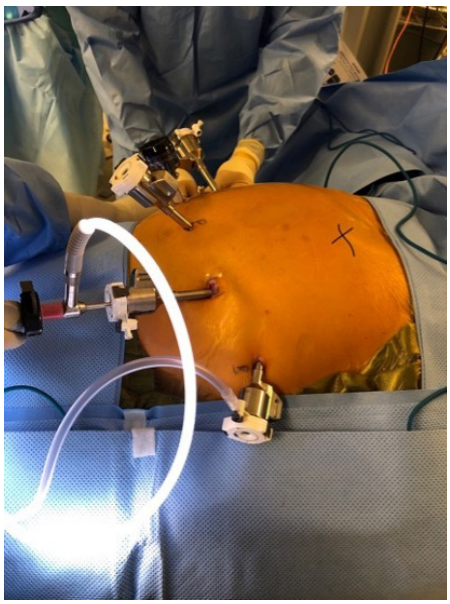

Figure 4 Robotic port placement for trans-hiatal robotic assisted laparoscopic duplication cyst excision and Dor fundoplication.

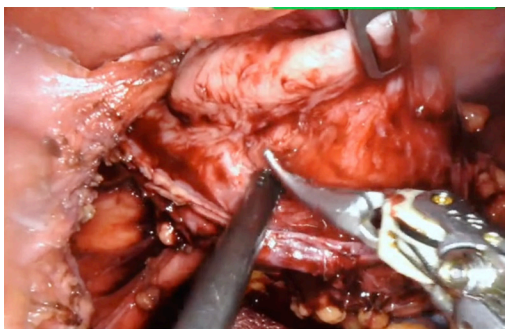

Figure 5 Myotomy and cyst enucleation.

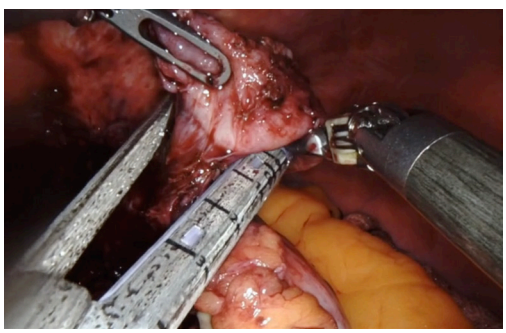

Figure 6 Cyst excision.

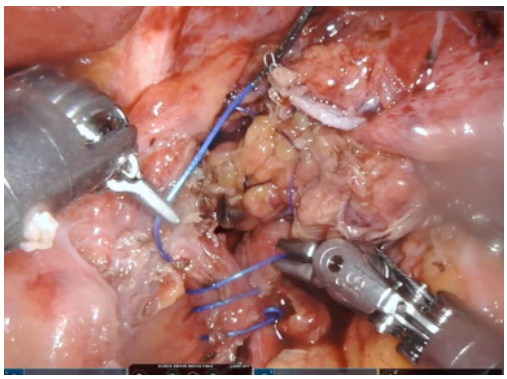

Figure 7 Posterior cruroplasty with running non absorbable 0 barbed suture.

are meticulous at visualizing and preserving both vagus nerves during the dissection. Thereafter, we dissect on the pars flacida towards the right crus preserving the peritoneal lining. We create a retro-esophageal window and utilize a Penrose drain for caudal and lateral traction. Finally, we mobilize the fundus by entering into the lesser sac. We take down the short gastric arteries with a combination of energy and hemostatic clips. We routinely extend our mediastinal circumferential esophageal dissection to the level of the inferior pulmonary veins, providing great exposure to the cystic mass. Thereafter, a myotomy is performed with blunt spreading and low energy. The myotomy is extended at least two centimeters proximally and distally to the cyst. Thereafter the cyst is enucleated with great care to avoid mucosal entry (*Figures 5,6*). Intraoperative evaluation with endoscopy and water and air tight test should be performed. A loose re-approximation of the myotomy is performed with 3.0 barbed absorbable sutures. A posterior cruroplasty with zero non absorbable barbed sutures is performed (*Figure 7*). If there is an associate large anterior defect, then an anterior cruroplasty is also performed. Finally, we perform a Dor fundoplication as it has been previously described (18) (*Figure 8*). If inadvertent mucosal entry were to happen and recognized intraoperatively, primary repair with 3.0 absorbable barbed sutures or interrupted PDS suture can be performed. We routinely perform an esophagram on post operative day #1, then begin patients on a liquid diet with discharge home within 48 hours of the index operation. Their diet is advanced at the follow-up appointment 1 week later.

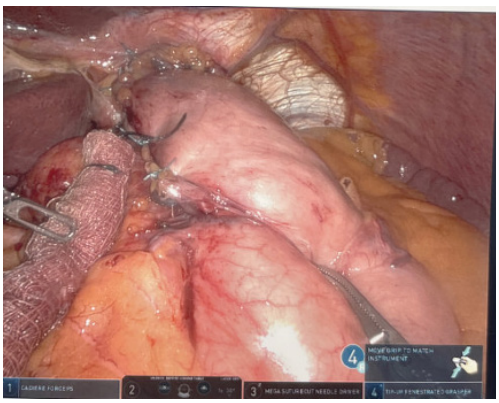

Figure 8 Anterior (Dor) fundoplication.

Summary

Esophageal duplication cysts of the esophagus are infrequent and mostly asymptomatic. However, they can cause complications later in life and shared decision making with patients regarding surgical excision is indicated. Historically open posterolateral thoracotomy has been described as the traditional approach to mediastinal cyst. Despite the adequate visualization and reach that this approach provides, it has been associated with significant post-operative pain and prolonged length of stay in the hospital (19). More recently, a minimally invasive technique including thoracoscopic and laparoscopic approaches have been shown to be safe and successful. At our institution we prefer a robotic assisted approach. The robotic platform not only provides with a three-dimensional view and digital imaging, but also increases dexterity particularly while dissecting and suturing in a reduced space like the hiatus. Moreover, the robotic platform provides the operating surgeon with unparalleled autonomy. One of the greatest advantages that this platform provides is the capacity to control your own camera and obtain the best angle of visualization during the entire dissection. This translates in reduce risk of mucosal injury, improving surgical outcomes (20).

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Review Article

The anesthetic management and the role of extracorporeal membrane oxygenation for giant mediastinal tumor surgery

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Abstract: Mediastinal tumors are a remarkably diverse category. They include malignant and benign forms with different rates of disease progression and tissue invasion. Anesthesiologists may encounter significant difficulties in managing patients with giant mediastinal tumors due to the non-negligible occurrence of severe cardiorespiratory collapse. Respiratory complications ensue from the compression of the airways induced by the mediastinal mass: the compressive effects may be exacerbated by positioning or anesthesia induction. Furthermore, the compression or invasion of major vessels may elicit acute cardiovascular collapse. The specter of sudden cardiorespiratory deterioration should lead the anesthesiologist to careful planning: acknowledging clinical and radiological signs that may presage an increased risk of life-threatening complications is of pivotal importance. This review aims to present a strategy for treating patients with mediastinal masses, starting with the pathophysiological elements and moving through preoperative care, intraoperative behavior, and the recovery period. We will also focus on respiratory and cardiovascular issues, emphasizing the need for extracorporeal membrane oxygenation (ECMO) as a rescue and crucial component of the anesthesia strategy. Understanding the physiological alterations after anesthesia induction can aid in identifying and treating potential problems. In addition, we attempted to offer insight into multimodal anesthesia and analgesia management: we emphasize the importance of a thorough preoperative assessment and the need for reviewing extracorporeal support not just a resuscitative strategy but as an integrated component of the perioperative care.

Keywords: Thoracic anesthesia; mediastinum; mediastinal tumor; extracorporeal membrane oxygenation (ECMO)

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Introduction

Mediastinal tumors are uncommon and represent a very heterogeneous group as they are populated by benign and malignant forms. Moreover, the histological variants of tumors vary widely between the adult and pediatric populations.

The anesthetic management of patients with giant mediastinal tumors is challenging due to the non-negligible incidence of severe cardiorespiratory adverse events. In a retrospective analysis of 117 pediatric patients with mediastinal masses, the rate of anesthesia-related complications was 9.4% (1). Adult patients have a similar incidence of perioperative adverse events. Béchard and colleagues demonstrated 3.8% intraoperative cardiorespiratory complications and 10.5% postoperative respiratory complications in their analysis of 105 patients (2).

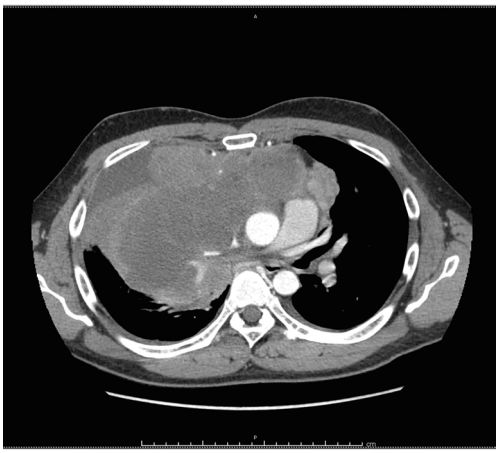

Figure 1 CT image of a 36-year-old male with non-Hodgkin's lymphoma adhered to the pleura and pericardium and with signs of bronchial and vascular compression. CT, computed tomography.

In addition, general anesthesia causes physiological changes that can exacerbate cardiorespiratory collapse. Therefore, a multidisciplinary approach is mandatory from the preoperative to the postoperative phase to avoid life-threatening situations.

This review aims to provide an approach to the patient with mediastinal mass starting from the pathophysiological aspects, passing through the preoperative management, the intraoperative conduct, and the postoperative phase. In addition, we will focus on respiratory and cardiovascular complications, highlighting the role of extracorporeal membrane oxygenation (ECMO) as an integrated part of the perioperative management.

The anesthesiologist's approach varies according to the type of planned surgical procedure. Therefore, our review aims to provide insight into the perioperative planning of patients undergoing major mediastinal surgery, leaving aside minor procedures.

Mediastinal Mass Syndrome (MMS) pathophysiology

MMS is the clinical expression of cardiorespiratory effects induced by mediastinal masses (3). These effects are enhanced by general anesthesia, which can be by itself the element of decompensation.

Respiratory complications

Respiratory complications are due to mechanical compression and/or tumor infiltration at the level of the tracheobronchial tree. Airway compression is responsible for specific signs and symptoms: cough, dyspnea, stridor, and hoarseness. The display of these symptoms is undoubtedly a warning sign for the anesthesiologist. Nevertheless, paucisymptomatic or asymptomatic patients may experience acute decompensation due to anesthesia induction as well (4). Therefore, the absence of preoperative symptoms does not exclude the risk of catastrophic intraoperative events (5). Anesthesia can exacerbate the compressive effects induced by mediastinal tumors through several mechanisms. A supine position is often required for induction of anesthesia or during surgery. It raises the compression of mediastinal structures by the gravitational effect. It also causes a cephalic displacement of the diaphragmatic dome, increasing intrathoracic pressure promoting airway compression, and impairing ventilation. Finally, the supine position increases the central blood volume, which may facilitate the volumetric increase of highly vascularised tumors. The induction of anesthesia is another critical point. The reduction of muscle tone favors the cephalad movement of the diaphragm and airway smooth muscle relaxation. This increases the risk of airway compression, mainly in the pediatric population, due to the more collapsible tissues (6).

The loss of spontaneous breathing can promote the onset of respiratory complications. Positive pressure ventilation increases pleural pressure, strengthening the compression of mediastinal structures. Poiseuille's law states that the flow resistance is directly proportional to the fourth power of the radius when the cross-section of the airway is reduced. In this case, post-stenotic turbulent flow is produced via positive pressure ventilation. Although air can overcome the stenotic airway due to the positive pressure, it cannot be completely flushed out during the expiratory phase due to the obstruction and the lack of laminar flow, which impede gas exchange and encourage the genesis of air trapping phenomena.

Hemodynamic complications

The hemodynamic imbalance is due to compression or infiltration of the heart or major vessels (*Figure 1*). The compression of the pulmonary artery is uncommon, thanks to the protection provided by the tracheobronchial tree. Patients are often paucisymptomatic, sometimes presenting only exertional dyspnea. The induction of anesthesia with reduced venous return, increased pleural pressure (due to

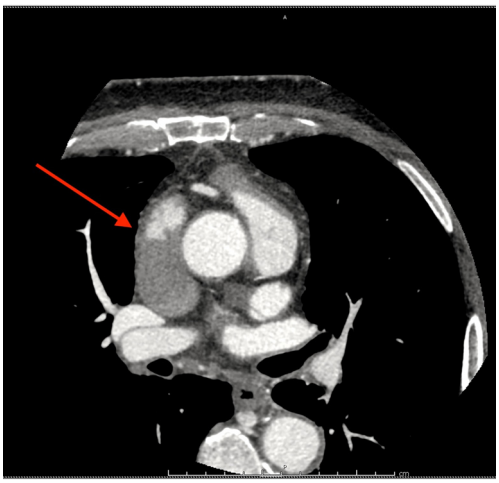

Figure 2 CT image of invasion and occlusion of superior vena cava extending up to the right atrium in a 72-year-old patient with malignant thymoma (red arrow). CT, computed tomography.

positive pressure ventilation), and the supine position may exacerbate right ventricular failure. Conversely, the superior vena cava (SVC) is more easily affected due to its location and low intravascular pressure. The obstruction of venous return from SVC generates superior vena cava syndrome (SVCS). The increased venous pressure in the upper body can result in edema of the pharynx and larynx with the onset of coughing, stridor, dyspnea, and dysphagia up to cerebral edema with headaches and mental confusion. Obstruction of venous return generates jugular turgor and in chronic forms the development of vascular networks allowing blood drainage into the inferior vena cava. SVCS occurs annually in about 15,000 people in the United States (7). Mediastinal tumors represent the most frequent malignant cause after non-small-cell and small-cell lung cancer (7). An Italian retrospective analysis of patients with stage III thymic tumors showed 24.1% involvement of major vessels with 12.4% involvement of the SVC (8). The induction of anesthesia is once again a possible cause of decompensation. Lowering the patient's head increases hydrostatic pressure, magnifying cerebral edema. Furthermore, reducing systemic vascular resistance induced by anesthetic drugs may induce acute central hypovolemia, given the existing impairment of blood return from the SVC, which carries approximately one-third of the venous return to the heart (7).

Preoperative assessment

Clinical examination is the first step in evaluating a patient with mediastinal tumors. It is important to recognize signs and symptoms of cardio-respiratory involvement: dyspnea, coughing, stridor, hoarseness, syncope, and the patient's upper-body edema. Furthermore, it is essential to evaluate the variation of symptoms with the patient's position and to collect a detailed history of the patient's preferred and non-tolerated positions. A "rescue position" should be reported during the anesthetic assessment. Patient positioning may be the simplest and most effective intraoperative maneuver to resolve life-threatening cardio-pulmonary complications. This primary assessment provides an initial grading of anesthesia risk: Anghelescu and colleagues demonstrated that orthopnea and upper body edema were significantly associated with anesthetic complications (1). Béchard and colleagues obtained similar results in adults: severe cardiorespiratory signs and symptoms were strongly associated with perioperative complications (2).

Radiological imaging is an essential adjunct in the preoperative evaluation of patients with giant mediastinal tumors. Computed tomography (CT) is the standard imaging technique. It is a rapid examination, possible to perform even in patients with poor supine tolerance. CT scan has a high sensitivity in assessing airway diameter, and the administration of contrast material allows accurate assessment of compression or thrombosis of the SVC (*Figure 2*). Reduction of the tracheal cross-sectional area (CSA) is a strong predictor of perioperative respiratory complications. An airway CSA, less than 50% of the standard diameter, seems to be associated with an increased risk of postoperative severe respiratory complications (2). A retrospective analysis of children with anterior mediastinal masses demonstrated a high risk of intraoperative respiratory complications in patients with either an isolated tracheal CSA less than 30% of normal or a tracheal CSA less than 70% associated with carinal or bronchial compression (9). Fiberoptic tracheobronchoscopy is another effective technique to assess airway compression or infiltration but, it should be performed in selected cases as the airway partial occlusion caused by the instrument might be itself a cause of clinical derangement. Pulmonary function tests have been extensively used in the preoperative phase, though they demonstrated a low sensitivity in the prediction of intraoperative respiratory complication. Nevertheless, Béchard and colleagues demonstrated that a peak expiratory flow of less than 40% was associated with a more than 10-fold increase in the risk of postoperative respiratory complications (2).

A comprehensive echocardiographic examination should

be performed in all patients with signs or symptoms of SVCS or suggestive CT scan imaging. Echocardiographic evaluation may help excluding signs of pericardial effusion and providing information on biventricular systolic and diastolic function: good biventricular function ensures greater functional reserve in case of sudden hemodynamic changes (10). The preoperative assessment should ultimately provide a classification of anesthesia risk. We can classify patients into risk classes: *safe*, *uncertain*, and *unsafe* (3).

Preoperative planning is the cornerstone in managing patients with giant mediastinal masses. Perioperative discussion should involve anesthesiologists, surgeons and oncologists. All professionals should agree on the proposed treatment and alternative strategies in case of intraoperative drawbacks. Creating a multidisciplinary discussion may reduce the risk of life-threatening complications (11).

ECMO prediction

ECMO is used to treat severe cardiopulmonary failure, but it is not yet known whether it is also appropriate for use in patients with cancer. Thoracic neoplasms are distinct from other malignant tumors because they may have a direct effect on cardiopulmonary function, nevertheless as observational and registry analysis could not provide a clear recommendation pro or contra ECMO application, focus on tailored patient selection should pursued to achieve optimal results (12-14).

The preoperative phase should also identify patients at high risk of respiratory or hemodynamic collapse who could benefit from extracorporeal support. In recent years, many case reports have been published on the use of intraoperative ECMO in patients with mediastinal tumors (15,16). In addition, extracorporeal support has also been used to ensure the initial stages of chemotherapy in selected patients (17-19). The feasibility of ECMO support in cancer surgery is acknowledged (20). However, extracorporeal support is often started in emergency conditions as a rescue therapy. In 2011 a systematic review of lung resections for non–small cell lung cancer under extracorporeal support demonstrated that survival was significantly higher when placement on bypass was planned as opposed to unplanned or emergency placement (21). These data confirm the need for preoperative planning to identify patients who may benefit from extracorporeal support. Recently, Leow *et al.* (16) and Ramanathan and colleagues (22) proposed an algorithm to identify patients with mediastinal masses potentially eligible for ECMO. They individuated high-risk patients in the case of:

(I) Acute SVCS;
(II) Pulmonary artery or right ventricular outflow tract obstruction;
(III) Airway compression >50%;
(IV) Cardiac or great vessel involvement/invasion with possible need for cardiac or vascular excision or reconstruction.

However, identifying patients with acutely decompensated SVCS who could benefit from ECMO support is not straightforward. Recently, Potere and colleagues evaluated the possible creation of a scoring system to assess the use of ECMO in patients with SVCS (23). Patients with a radiological score of II or higher (according to the classification of Qanadli *et al.* (24) and a grade II or higher in the symptoms classification of Yu *et al.* (25) should be considered candidates for ECMO (*Tables 1*,*2*).

Moreover, high-risk patients should receive multidisciplinary planning to decide between a veno-venous or veno-arterial ECMO approach. Veno-arterial ECMO should be preferred in compromised patients with giant mediastinal masses and high risk of respiratory and hemodynamic collapse. Therefore, veno-venous ECMO should be applied in selected cases of patients with isolated respiratory symptoms and airway compression.

In all patients with at least one of the former risk factors, femoral vein/femoral artery sheaths should be inserted (depending on the type of ECMO setup chosen) before the induction of anesthesia. Perfusionists should be available in the operating room for the whole duration of surgery with a primed ECMO machine. Conversely, in patients with more than one risk factor, preoperative cannulation with the start of extracorporeal circulation before anesthetic induction should be strongly advocated.

Intraoperative management

Patients with giant mediastinal tumors need an endorsed multidisciplinary approach to achieve the best intraoperative conduct. The anesthetic approach should be tailored to the patient's risk class and the need for possible ECMO support. Patients classified as *safe* should receive the same care dedicated to major thoracic surgery. Nonetheless, as already pointed out, anesthesia induction and intrathoracic pressure changes may exacerbate a cardiorespiratory collapse even in asymptomatic patients.

The anesthesiologist should escort all *unsafe* patients to the operating theatre. Before induction of anesthesia, a

Table 1 Radiological classification of superior vena cava obstruction according to Qanadli *et al.* (24)

Types	Degree of SVC obstruction
Type I	Stenosis of SVC up to 90%
Type II	90–99% of SVC stenosis
Type III	Complete obstruction of SVC
Type IV	Complete obstruction of SVC and at least one major tributary

SVC, superior vena cava.

Table 2 Symptomatic classification of superior vena cava obstruction according to Yu *et al.* (25)

Grade	Category	Definition
0	Asymptomatic	Radiographic signs of SVC obstruction, but no symptoms
1	Mild	Mild edema in head or neck, cyanosis or plethora
2	Moderate	Edema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw or eyelid movements, visual disturbances caused by ocular edema)
3	Severe	Mild or moderate cerebral edema (headache, dizziness) or mild/moderate laryngeal edema or diminished cardiac reserve (syncope after bending)
4	Life-threatening	Significant cerebral edema (confusion, obtundation) or significant laryngeal edema (stridor) or significant hemodynamic compromise (syncope without precipitating factors, hypotension, renal insufficiency)
5	Fatal	Death

SVC, superior vena cava.

safety checklist should be follow:

(I) Vascular access: in all cases of SVCS, the placement of vascular accesses in tributary vessels of the SVC should be avoided to reduce thrombosis risk and to ensure the proper onset of administered drugs. The insertion of a large-bore femoral vein catheter and a femoral artery catheter should be achieved. The femoral venous catheter should be inserted distally when placing a femoral vein sheath or cannulation for ECMO or on the other limb. The risk of significant hemorrhages during mediastinal surgery dramatically increases in patients with SVCS (7,26). For this reason, the placement of a rapid infusion catheter (RIC) in a lower limb vessel is recommended.

(II) Airway management is always a challenge. Indeed, even without symptoms or radiological signs of airway compression, supine positioning and anesthesia induction can lead to critical airway stenosis. Therefore, the availability of various airway management devices is obliged: video laryngoscope, flexible fiberscope, rigid bronchoscope, and reinforced and double-lumen endotracheal tubes. In our opinion, well-trained thoracic anesthesiologists and experienced bronchoscopists should be available for the duration of the surgery. Moreover, perfusionists and a primed ECMO machine should always be accessible, even in unexpected cases.

(III) Anesthetic monitoring:

- (i) Hemodynamic monitoring: transpulmonary thermodilution systems or pulse-contour analysis to monitor cardiac function continuously should be applied;
- (ii) Transesophageal echocardiography (TEE) should be used when available especially in previously evaluated patients with systolic or diastolic dysfunction, pericardial effusion, signs of heart compression or masses (*Figure 3*);
- (iii) Near infrared spectroscopy (NIRS) monitoring to assess any worsening of the SVCS-induced cerebral edema;
- (iv) Right arm pulse oximetry to evaluate possible injuries to the brachiocephalic trunk.

Induction of anesthesia requires a stepwise approach. Depending on local protocols and anesthesiologist's

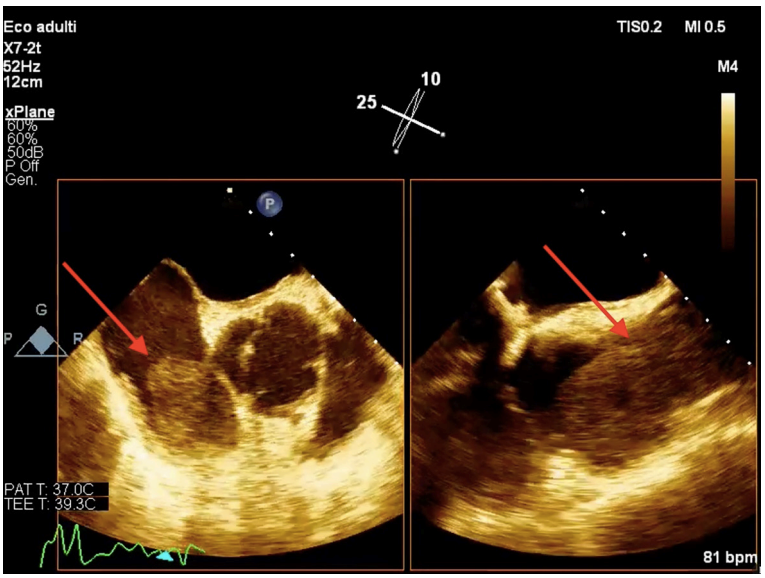

Figure 3 Transesophageal echocardiography image of tumoral invasion of superior vena cava and right atrium in a 72-year-old patient with malignant thymoma (red arrows). PAT T, patient's temperature; TEE T, transesophageal echocardiography probe temperature; TIS, Soft Tissue Thermal Index; MI, Mechanical Index.

experience, an effective way to secure the airways is awake fiberoptic intubation with the patient in spontaneous breathing. Topic anesthesia and intravenous drugs with a short half-life (remifentanil, dexmedetomidine, ketamine) guarantee the achievement of oro-tracheal intubation with an excellent level of security. Remifentanil boluses that could exacerbate stiffness, compromising patient ventilation and subsequent intubation should be avoided.

The endotracheal tube should be the largest possible to resist extrinsic compressions. We may use spiral-reinforced endotracheal or dual-lumen tubes if the surgeon requires them. Subsequently, the anesthetic plan should be deepened gradually to keep the patient breathing spontaneously. The maintenance of spontaneous breathing or pressure support ventilation avoids a significant increase in pleural pressure, decreasing the compressing effects of the mediastinal mass.

Nevertheless, as surgery often requires neuromuscular blockade, using short-acting paralyzers, such as succinylcholine or rocuronium, as its antidote; sugammadex is currently available seems a convenient choice to return to spontaneous ventilation in case of severe airway collapse or hemodynamic instability.

Recently, Hartigan and colleagues demonstrated that neuromuscular blockade did not induce airway collapse or difficult ventilation in patients with mediastinal masses presenting different grades of airway stenosis (27). Nevertheless, the study included only seventeen patients. Furthermore, patients could be excluded from the study according to the attending anesthesiologists' choice, maybe creating a selection bias.

If the loss of spontaneous breathing exacerbates cardiorespiratory collapse in fact, the first step should be the rapid reversal of neuromuscular blockade. Meanwhile, the patient should be placed in her/his "rescue position" (if there is one), and ventilation should be attempted using a rigid bronchoscope. Unfortunately, a rigid bronchoscope can overcome tracheal compression but it hardly restores adequate ventilation in case of compression at the level of the bronchial branches.

Cardiorespiratory collapse may appear even in spontaneous breathing patients placed in their safety position. In this case, excluding a displacement of the endotracheal tube, an anesthetic plane too deep, or intraoperative bleeding, a common complication in patients with SVCS, is mandatory. Therefore, when all the reversible causes have been ruled out and treated, only two rescue therapies remain for the clinicians: the elevation of the mediastinal mass by the surgeon (sometimes with emergent sternotomy) or the extracorporeal support (veno-venous ECMO or veno-arterial ECMO). However, as already pointed out, ECMO support should be planned in the preoperative phase and not considered the last resource.

Postoperative management

Safe patients should be promptly extubated at the end of surgery and require sub-intensive care monitoring for at least 24 hours in case of no intraoperative complications.

Patients classified as *unsafe* or *uncertain* should be monitored in the intensive care unit after surgery. Achieving rapid postoperative extubation to avoid complications related to invasive ventilation (i.e., ventilator-associated pneumonia) and ensure rapid access to the rehabilitation phase or the start of chemo-radiotherapy should be pursued. Nevertheless, adequate pain management is essential to ensure rapid extubation and rehabilitation. One of the most effective approaches is multimodal and opioid-sparing analgesia (28). Several medications in combination with local anesthetics seem to have a good profile in reducing the opioids needed after thoracic surgery: ketoprofen, ketorolac, paracetamol, pethidine, flurbiprofen, dexmedetomidine (29). Among others, ketamine demonstrated a statistically significant reduction in acute post-thoracotomy pain but low power as a preventative agent for chronic post-thoracotomy pain (30) as well as pregabalin significantly reduced pain scores, decreasing postoperative neuropathic pain and morphine consumption (31).

The multimodal approach to analgesia involves regional anesthesia techniques. Thoracic epidural analgesia has been the gold standard for perioperative post-thoracotomy pain management (32). However, it is burdened by the risk of hypotension and the inability to place the epidural catheter in patients with impaired coagulation status. The search for less invasive and safer techniques is then advocated. The erector spinae plane (ESP) block might be the regional anesthesia technique of choice for the patient. It carries a low-risk profile, far from the pleura, spinal cord, and major blood vessels (32). It can be performed with high safety even in patients with impaired coagulation, and it demonstrated similar pain relief effects compared to thoracic paravertebral block (33). In a randomized controlled trial conducted on sixty patients, ultrasound-guided ESP block exhibited a significant analgesic and opioid-sparing effect in patients undergoing thoracotomy surgery (34).

Conclusions

We aimed to provide a pathophysiological view of anesthesia-induced changes in patients with giant mediastinal tumors. Understanding the physiological changes induced by anesthesia can help prevent and treat possible complications. In addition, we tried to provide an insight into different and multimodal approaches, stressing the need for a detailed preoperative phase and the need to consider extracorporeal support not as a rescue therapy but as an incorporated part of perioperative management.

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Footnote

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Review Article

Imaging modalities (MRI, CT, PET/CT), indications, differential diagnosis and imaging characteristics of cystic mediastinal masses: a review

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Abstract: Cystic mediastinal masses have traditionally represented a diagnostic dilemma with differentiation of malignant masses a particular area of concern. Each imaging modality has strengths and weaknesses in mediastinal imaging—computed tomography (CT) offers increased spatial resolution at the cost of poorer soft tissue differentiation and requiring ionizing radiation, while magnetic resonance imaging (MRI) offers superior soft tissue contrast/characterization at significantly greater cost. Ultrasound offers real-time visualization but is operator and tissue dependent. [18F]fluoro-D-glucose (F-18 FDG) positron emission tomography (F-18 FDG PET) CT provides functional information, but poorer spatial resolution. Recent advances have focused upon the use of magnetic resonance imaging to aid in characterization of cystic mediastinal lesions, particularly in the context of indeterminate CT findings. The mediastinum may be divided into three anatomic compartments: prevascular, visceral, and paravertebral. All three compartments extend superiorly from the thoracic inlet and inferiorly to the diaphragm. These compartments provide a useful framework for categorizing normal and pathologic mediastinal processes. In this article, we will review the imaging characteristics of mediastinal cystic lesions via a case-based review divided by anatomical mediastinal compartments. Characteristic imaging features and troubleshooting are particular areas of focus. Normal variants that may mimic cystic pathology are discussed. The roles of CT and MRI will be emphasized. Cases from our institution are presented as illustrative examples.

Keywords: Mediastinum; magnetic resonance imaging (MRI); computed tomography (CT); ultrasound; cystic lesions

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Introduction

Mediastinal cystic lesions are typically well-marginated, rounded or oval shaped lesions filled with fluid and lined with epithelium. While most mediastinal cystic masses are benign (duplication cysts, pericardial cysts, thymic cysts, teratomas, meningoceles, lymphangiomas, etc.), several tumors may initially present with a cystic component or undergo cystic degeneration, including lymphoma, thymoma, teratoma and nodal metastases.

The differential diagnosis of cystic mediastinal lesions can be divided by location using the tricompartmental definition by Carter *et al.* and the International Thymic Malignancy Interest Group using cross-sectional imaging (1). This mediastinal compartment classification divides the mediastinum into three compartments: the prevascular compartment, the visceral compartment, and the paravertebral compartment. All three compartments extend superiorly from the thoracic inlet and inferiorly to the level of the diaphragm. The prevascular compartment includes all structures posterior to the sternum and anterior to the pericardium. The visceral compartment includes all

structures from the posterior boundary of the pre-vascular mediastinum to a vertical line connecting each thoracic vertebral body 1 cm posterior to their anterior margins. The paravertebral compartment includes all structures posterior to the posterior boundary of the visceral compartment to a vertical line along the posterior margin of the chest wall at the lateral margin of the transverse process of the thoracic spine.

Depending on the content of the cyst (simple fluid, protein, or blood products) imaging characteristics on computed tomography (CT) and magnetic resonance imaging (MRI) will vary. Often, lesions in the mediastinum have density above water ranging between 20 and 100 Hounsfield units (HU) and are therefore inconclusive for solid lesions versus complicated cysts. MRI is essential to distinguish solid from cystic lesions as well as for the evaluation of septations or solid components. Differentiation of benign and malignant lesions can be challenging. In addition to a thorough clinical history and physical examination, familiarity with the imaging patterns of mediastinal cysts is critical to differentiating benign and malignant lesions.

Imaging modalities

Role of CT

CT is often the modality by which mediastinal lesions are first identified and characterized. Characteristics of simple cysts on CT include low density (0 to 20 HU), thin (imperceptible) walls, few or no septations, and lack of contrast enhancement. CT provides two major advantages over MRI and US, namely rapid acquisition, and excellent spatial resolution of mediastinal structures. However, soft tissue contrast is poor, and identification of lesion margins can be difficult, even in contrast-enhanced studies. Cystic lesions (proteinaceous, infected, or hemorrhagic) in the mediastinum can be misinterpreted as solid due to cellular debris or blood products with resultant internal densities ranging between 20 and 100 HU. Masses with dense calcifications may obscure underlying soft tissue detail due to blooming artifact. Enhancing septations, indicative of increased vascularity, may be a herald of malignancy. Dual-energy CT with intravenous contrast can help differentiate cystic from solid lesions with material decomposition techniques using digital subtraction of iodine (intravenous contrast). This allows differentiation of tissue enhancement from hemorrhagic/proteinaceous fluid as well as differentiation of calcium from contrast accumulation. Although there is scarcity of literature regarding the use of this technique in the evaluation of mediastinal masses, it is likely to play an important role in characterization of mediastinal lesions in the future.

Role of MRI

Magnetic resonance imaging is a key problem-solving tool for the characterization of mediastinal cystic masses. Unlike CT, MRI can more clearly characterize soft tissue lesions and identify infiltrative disease. Diffusion weighted imaging can identify lesions mimicking cysts, as cellular content/debris will cause diffusion restriction in comparison to simple cysts, which will not. Gadolinium contrast further allows characterization of lesion vascularity and enhancement. In and out of phase imaging allows identification of microscopic fat which is commonly seen in normal or hyperplastic thymic tissue. While MRI does not expose the patient to ionizing radiation, its cost and increased acquisition times are a drawback.

MRI is the preferred next step after an indeterminate CT, particularly to determine enhancement, identification of microscopic fat, and visualization of fine soft tissue detail (nodularity, septations). For example, MRI can readily differentiate hyperdense cysts from solid masses. In addition, when calcifications cause obscuring hyperdensity on CT, MRI will be unaffected. In various clinical scenarios, characteristic MR findings can make a certain diagnosis without the need for tissue sampling.

Strengths of MRI include differentiation between cystic and solid lesions, evaluation of simple versus complex cystic lesions, evaluation for restricted diffusion (seen on infection due to high cellular debris), and evaluation for the presence of blood products or contrast enhancement. As with CT, enhancing (vascular) septations can be a sign of malignancy. Furthermore, due to its high tissue contrast, invasion of adjacent soft tissue structures is well evaluated with MRI.

MRI of the mediastinum should, at a minimum, include in-and-out of phase T1, T1 weighted pre-and-post contrast, T2 weighted, and diffusion weighted sequences (2,3). Simple cysts will demonstrate smooth, thin walls with internal T1 hypointensity, T2 hyperintensity, and no diffusion restriction or contrast enhancement. Benign cysts may demonstrate intermediate or T1 hyperintensity if hemorrhagic or proteinaceous. T1 pre and post contrast sequences (with subtraction if available) are key. If a cystic lesion contains solid, enhancing components, there is a much higher suspicion for malignancy. T2 hyperintense

cysts are typically benign, since this indicates simple fluid, though many benign lesions will be T2 intermediate if bloody and/or proteinaceous. If only thin septations are present, or the cyst is unilocular, the lesion is also likely benign. In these cases, imaging follow-up may be beneficial to confirm benign behavior. Note that acquired thymic cysts, which are benign lesions, characteristically are multiloculated.

Diffusion weighted imaging aids in the characterization of mediastinal lesions. Cystic lesions will not demonstrate diffusion restriction unless infected. As such, a restricting lesion must either represent a solid lesion or an infected cyst. Comparison should be made to the apparent diffusion coefficient (ADC) maps, as T2 shine-through may mimic restriction on the diffusion weighted imaging (DWI) images. Simple fluid will also be bright on the ADC map, while truly restricting lesions will be dark.

Role of F18-FDG PET CT

F18-FDG PET CT has a limited role in the characterization of mediastinal cystic lesions. F18-FDG PET CT will identify hypermetabolic lesions, though numerous studies have shown low specificity as benign lesions can show similar degrees of hypermetabolism (4-7). Simple and benign cystic lesions should not demonstrate internal hypermetabolism, however it might be present in the setting of superimposed infectious or inflammatory condition. Other limitations include low spatial resolution, with the risk of small lesions not being detected despite their malignant nature as well as ametabolic malignant lesions. Specialized positron emission tomography (PET) studies with individualized radiotracers may be utilized on a case-by-case basis for metastatic lesions, neuroendocrine lesions, and other suspected malignancies.

Role of ultrasound

Transthoracic mediastinal ultrasonography can be effective in the characterization of mediastinal masses. B-flow imaging allows the visualization of flow and microbubble contrast can be safely administered to all patients (contrast-enhanced ultrasound, CEUS). The European Federation of Societies for Ultrasound in Medicine and Biology includes CEUS in its armamentarium for mediastinal imaging (8). An additional benefit of ultrasonographic imaging is its ability to be used for procedural guidance.

Simple cysts are characteristically regular, thin/imperceptibly walled anechoic structures with posterior acoustic enhancement. Internal vascularity should be absent. Microbubble contrast, which has virtually no contraindications, may be used to further assess intralesional flow. Thick septations, solid components, internal vascularity, and irregular marginations are suspicious for malignancy.

Approach to imaging

In general, contrast-enhanced CT is the workhorse modality for characterization of virtually all mediastinal cystic lesions. In indeterminate cases, MRI can be used for troubleshooting and further characterization. Ultrasound can be utilized without risk to the patient but is limited by operator ability and depth of target lesion. F18-FDG PET CT can be used in select cases in which functional imaging may elucidate underlying lesion characteristics.

Mediastinal cysts—catalogue

The mediastinal compartment of origin can help in the differential diagnosis of cystic mediastinal lesions; however, multiple lesions can be seen involving all three compartments. For example: Malignant or infectious necrotic lymphadenopathy, lymphangiomas, hemangioma, abscess formation, hematoma, and mesothelial cysts can be found in all three compartments. The combination of typical location and imaging characteristics can often lead to a confident radiologic diagnosis without the need for tissue sampling.

Pre-vascular compartment lesions

Thymic origin lesions are the most common cystic entity found in the prevascular mediastinum (4). In general, when a simple or hemorrhagic/proteinaceous cyst without solid enhancing nodularity or thick enhancing septations are present, the most likely diagnosis is thymic cyst followed by lymphangioma.

Thymic cysts

Thymic cysts have been described as rare lesions, though reports have found them to represent up to 28.6% of mediastinal cysts and 3.7% of all mediastinal masses (9). Congenital thymic cysts are rarer than acquired thymic cysts (*Figure 1*), which tend to have a thicker wall and be multilocular secondary to inflammation or hemorrhage

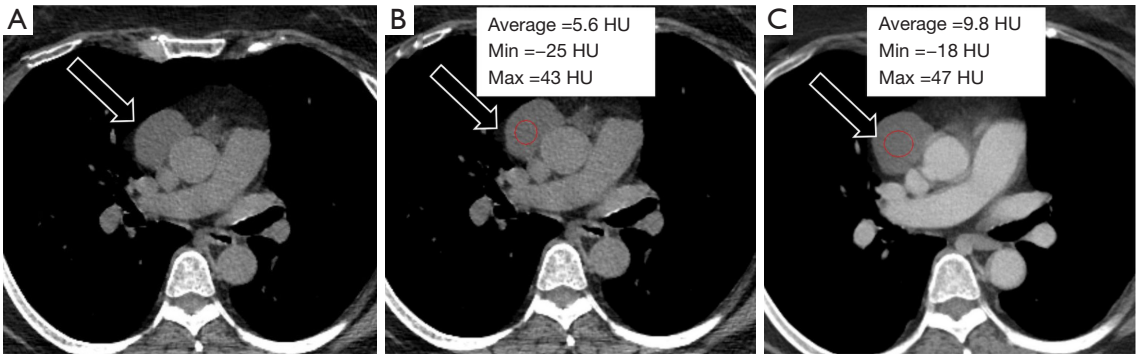

Figure 1 62-year-old female with a thymic cyst. CT imaging demonstrates a low-density lesion in the prevascular mediastinal compartment (A and B, black arrow; circle, average HU =5.6). Contrast administration subtlety increases the apparent density of the lesion, but a region of interest confirms persistent fluid-attenuation of the lesion (C, black arrow and circle, average HU =9.8). This lesion was compatible with a thymic cyst on pathology. CT, computed tomography; HU, Hounsfield unit.

(*Figure 2*). Thymic cysts can coexist with thymic hyperplasia and thymic neoplasms. Thymic cysts are often difficult to differentiate from other mediastinal lesions. Typical imaging characteristics on CT include a prevascular midline lesion with oval or rounded shape, circumscribed with homogeneous attenuation (less than 100 HU) and that does not yield mass effect on adjacent structures. Not infrequently, these lesions have measured density over 20 HU due to hemorrhagic or proteinaceous components and can be confused for a solid mass on CT. In these cases, MRI often helps with problem solving.

Cystic thymoma

Approximately 40% of thymomas will demonstrate cystic degeneration. Like thymic cysts, a cystic lesion in the prevascular mediastinum which is oval or rounded, circumscribed and homogeneous in attenuation can represent a cystic thymoma (*Figure 3*). MRI is the imaging modality of choice to assess for subtle nodular components or enhancing septations which differentiate this lesion from a thymic cyst. In rare cases, thymomas may also demonstrate internal hemorrhage (*Figure 4*).

Approximately 90% of thymomas will demonstrate contrast enhancement on the first post-contrast sequence. Delayed post-contrast acquisitions will demonstrate enhancement in 100% of thymic neoplasms, though said enhancement may be subtle (10). For this reason, multiplanar subtraction images are recommended. Additionally, over half of thymomas will demonstrate a cystic component, though it will typically be less than the entirety of the lesion. The majority of benign thymic cysts will demonstrate fluid signal on T2WI, some will be of low or intermediate signal. Benign cysts should not demonstrate enhancement—if present, it may be septal or rim enhancement, never internal (10).

Given the overlapping imaging characteristics of a small subset of cystic thymomas and benign thymic cysts, lesions with less than fluid signal on T2WI and non-enhancement should undergo follow-up imaging to ensure stability (11).

Mature cystic teratoma

Mature cystic teratomas and dermoid cysts are characterized by multiple tissue densities within a single mass (*Figure 5*). However, in many cases, these may not be readily apparent on CT imaging. MR imaging demonstrating macro or microscopic fat can aid in diagnosis (12). Multiple fat-fluid levels are highly specific (2). Gross fat is often easier to identify than microscopic fat (2).

Lymphangioma

Lymphatic malformations are often found in the prevascular compartment but can arise in all three compartments. Lymphangiomas are often indeterminant on CT, mimicking cystic neoplasms or soft tissue masses (2,13). Lymphangiomas usually present as unilocular or multilocular cystic lesion of various densities and sizes. On MRI, lymphatic lesions are typically T2 hyperintense with variable T1 signal depending on the degree of proteinaceous content. Lymphatic malformations are often septated or contain multiple grouped tubular channels, each of which may demonstrate unique T1 signal characteristics. T2 weighted sequences with fat suppression can aid in

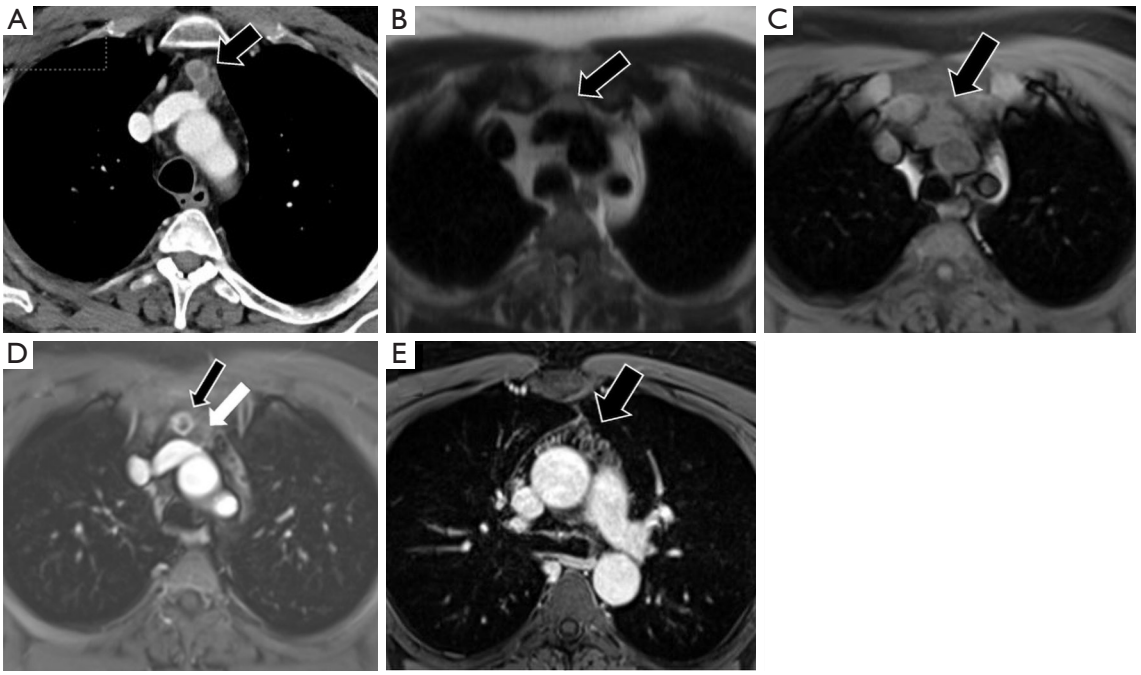

Figure 2 47-year-old male with a multiloculated (acquired) thymic cyst. CT images after the administration of contrast demonstrates multiple low-density lesions in the prevascular mediastinum (A). One of these lesions (black arrow) demonstrates peripheral high density. MRI evaluation of this lesion demonstrates intermediate to low T2 (B) and high T1 (C) signal compatible with hemorrhagic/proteinaceous components. After the administration of gadolinium, there is peripheral enhancement surrounding this lesion compatible with inflammatory changes in the capsule (D, black arrow). Other adjacent cystic lesions demonstrate simple fluid imaging characteristics and do not enhance after contrast (D, white arrow). Surrounding strands of residual thymic tissue are noted (E, black arrow). This lesion was consistent with a multiloculated thymic cyst on pathology. CT, computed tomography; MRI, magnetic resonance imaging.

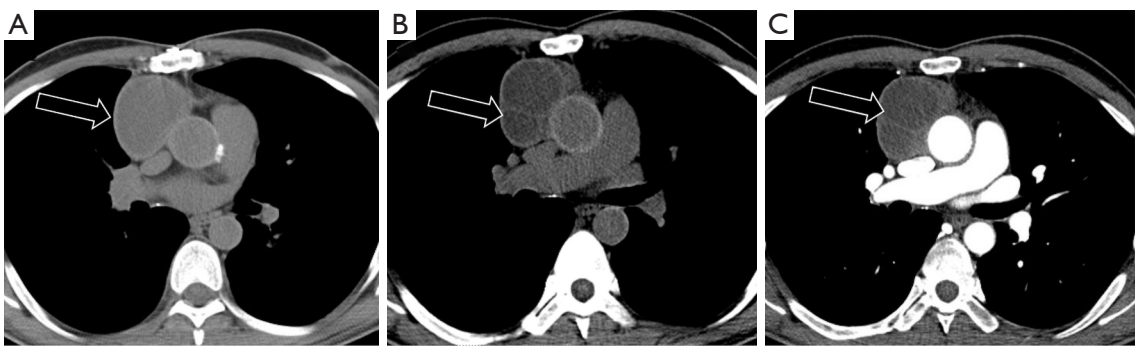

Figure 3 61-year-old male with a cystic thymoma. CT imaging demonstrates a well-circumscribed cystic lesion with minimal peripheral enhancement (A, black arrow). Thick internal septations (B, black arrow) that do not demonstrate definite enhancement (C, black arrow) are present. This is one such example in which MRI imaging would provide useful information to assess for an underlying solid mass or enhancing nodularity to corroborate cystic neoplasm. CT, computed tomography; MRI, magnetic resonance imaging.

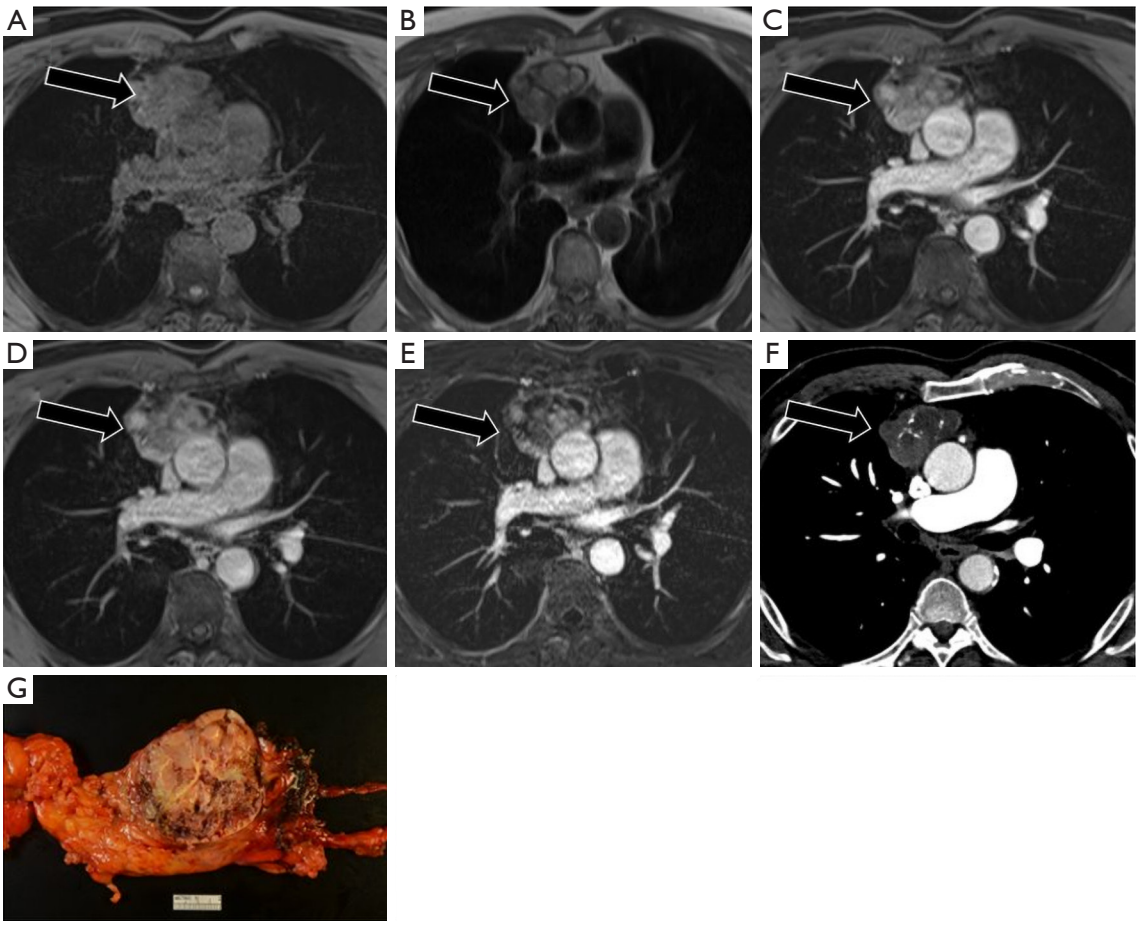

Figure 4 71-year-old-male with cystic and hemorrhagic thymoma. MRI shows a multicystic lesion (black arrow) with heterogeneous T1 signal (A), intermediate T2 signal (B), with heterogeneous internal enhancement and enhancing nodular septations (C) confirmed with delayed acquisitions (D) and subtraction (E). A contrast-enhanced CT shows enhancing internal septations (F), favoring thymic neoplasm over benign thymic cyst. Pathological specimen at time of resection (G). MRI, magnetic resonance imaging. CT, computed tomography.

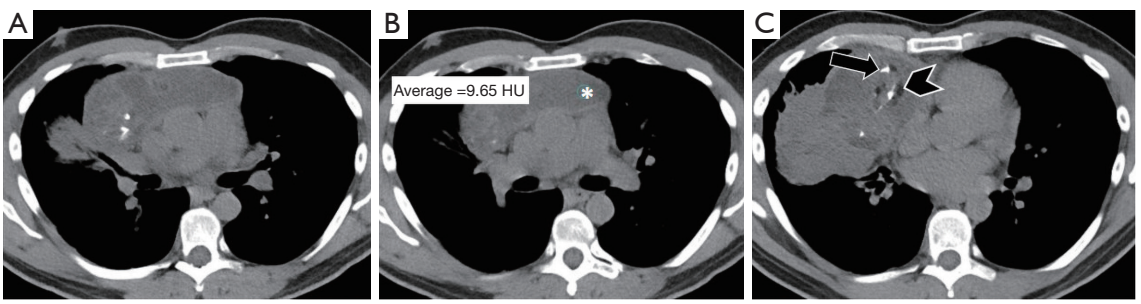

Figure 5 36-year-old male with a cystic teratoma. CT images without intravenous contrast demonstrated a large cystic and solid mass centered in the pre-vascular mediastinum (A). Note is made of areas of low-density (B, asterisk, HU =9.65; C, arrow) and high-density (C, arrowhead) compatible with fluid, fat deposition, and calcification, respectively. Pathology confirmed teratoma with cystic changes. CT, computed tomography; HU, Hounsfield unit.

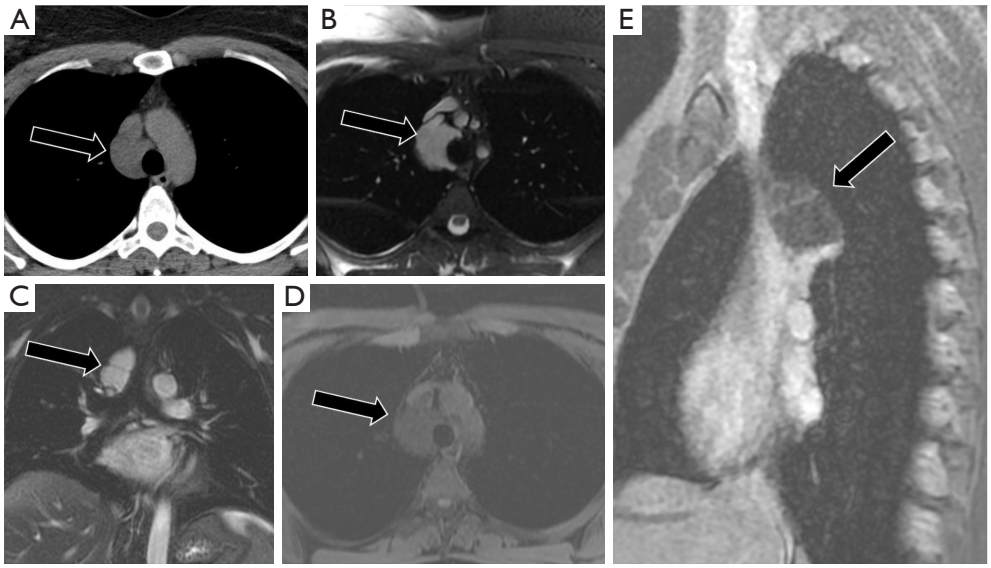

Figure 6 43-year-old female with lymphangioma. CT demonstrates a lobulated hypodense lesion in the visceral compartment (A, black arrow). MRI demonstrates a multiloculated T2W hyperintense (axial, B, black arrow; coronal, C, black arrow), T1 intermediate lesion (D, black arrow) with a thin enhancing septation (E, sagittal, black arrow), consistent with lymphangioma. CT, computed tomography; MRI, magnetic resonance imaging.

the identification of even non-dilated lymphatic channels (*Figure 6*). Lymphatic malformations may demonstrate mild enhancement secondary to contrast third spacing, or small venous channels. However, solid/nodular enhancing components should trigger further evaluation for malignancy.

Visceral compartment lesions

Foregut duplication cysts are one of the most common cystic lesions found in the visceral compartment. In this compartment, duplication cysts, pericardial cysts/diverticula, and lymphatic lesions are encountered.

Foregut duplication cysts

Foregut duplication cysts, one of the most common types of benign mediastinal cysts, can be further subdivided into neurenteric, bronchogenic, and esophageal cysts (2,14). Neurenteric cysts are persistent connections between the spinal canal and bowel. Bronchogenic cysts are abnormal ventral budding/branching of tracheobronchial tree lined by pseudostratified columnar epithelium. Esophageal cysts are outpouchings arising from the esophagus. Neurenteric cysts are more commonly found in the paravertebral compartment (see below), while bronchogenic and esophageal cysts originate in the visceral compartment. Differentiation of these lesions, which share similar imaging characteristics, is dependent upon location and communication with the tissues of origin.

As with other cystic lesions, foregut duplication cysts demonstrate CT hypodensity, T1 hypo-intermediate intensity, and T2 intermediate-hyper intensity depending on the degree of proteinaceous debris. Duplication cysts may become infected after intervention. In such cases, intermediate signal and thicker rim enhancement may be seen (*Figure 7*).

Pericardial cysts/diverticula

Pericardial cysts are functionally mesothelial cysts of the pericardium, most commonly found in the cardiophrenic angles (right greater than left). Both pericardial cysts and diverticula are caused by abnormal fusion of the mesenchymal lacunae, though diverticula retain communication with the pericardial space while cysts are isolated. Pericardial diverticula may change in size and shape with positioning, while cysts may grow slowly over time. Pericardial cysts account for up to 6% of all mediastinal masses and 33% of mediastinal cysts (15,16). Pericardial cysts are typically single, simple cysts—well-defined, low-density lesions on CT (30–40 HU), homogeneous T1 hypo/

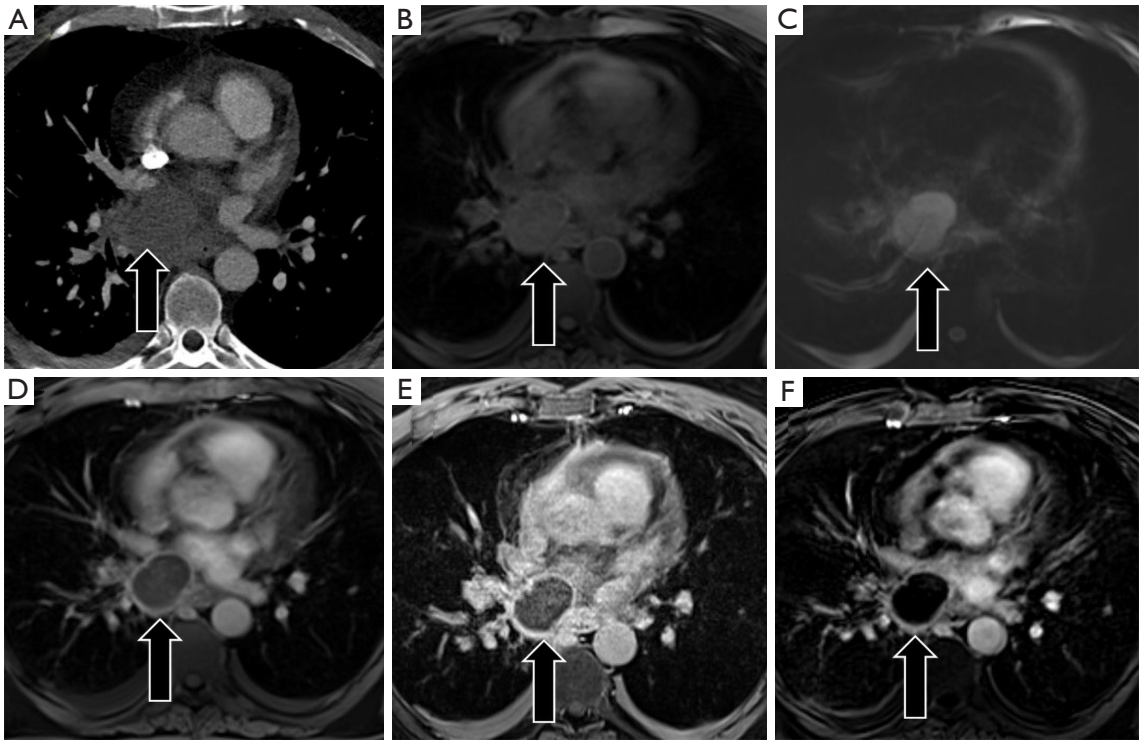

Figure 7 In this 47-year-old male, an esophageal duplication cyst underwent biopsy and subsequently developed an infection. Contrast-enhanced CT demonstrates a non-enhancing, intermediate density lesion in the visceral compartment (A, black arrow). MRI demonstrates intermediate to high T1 (B, black arrow) and high T2 signal (C, black arrow) within the lesion. After the intravenous administration of gadolinium, there is a peripheral capsular enhancement without internal septations or solid enhancing component (D and delayed acquisition E, black arrow). This is confirmed on subtraction images (F, black arrow). CT, computed tomography; MRI, magnetic resonance imaging.

T2 hyper (unless proteinaceous) (*Figure 8*).

Pericardial abscess/post-interventional collections

Abscesses can rarely arise in the pericardium, typically after surgical or percutaneous intervention. These lesions can mimic other cystic neoplasms.

Like abscesses in other anatomic locations, pericardial abscesses will be characterized by a rim-enhancing fluid collection that demonstrates T1 intermediate or low signal and T2 intermediate or high signal. Diffusion restriction is characteristic. A history of recent pericardial intervention is beneficial in confirming the diagnosis (*Figure 9*).

Mycetoma

In addition to mediastinal abscesses, other infectious collections may be encountered in the mediastinum. Fungal mycetomas demonstrate similar imaging characteristics to abscesses (*Figure 10*). A thorough clinical history with focus upon exposure history and potential causes of immunocompromise can be beneficial. For example, the illustrated case was of a patient with histoplasmosis with immunocompromise secondary to hematologic malignancy and a history of spelunking in endemic regions.

Paravertebral compartment lesions

Paravertebral compartment lesions are most likely neurogenic in origin (17). Cystic lesions of neurogenic origin include meningocele, cystic schwannoma, and neurenteric cysts.

Meningocele

Meningoceles are anomalous paravertebral cystic masses that result from leptomeningeal herniation into an intervertebral foramen or a vertebral body defect. In the former, the intervertebral foramen can be widened. Meningoceles will follow cerebrospinal fluid (CSF) intensity on MRI sequences—T1WI hypointensity and T2WI hyperintensity (18). Often, cystic neurogenic lesions can mimic meningoceles. However, communication with the

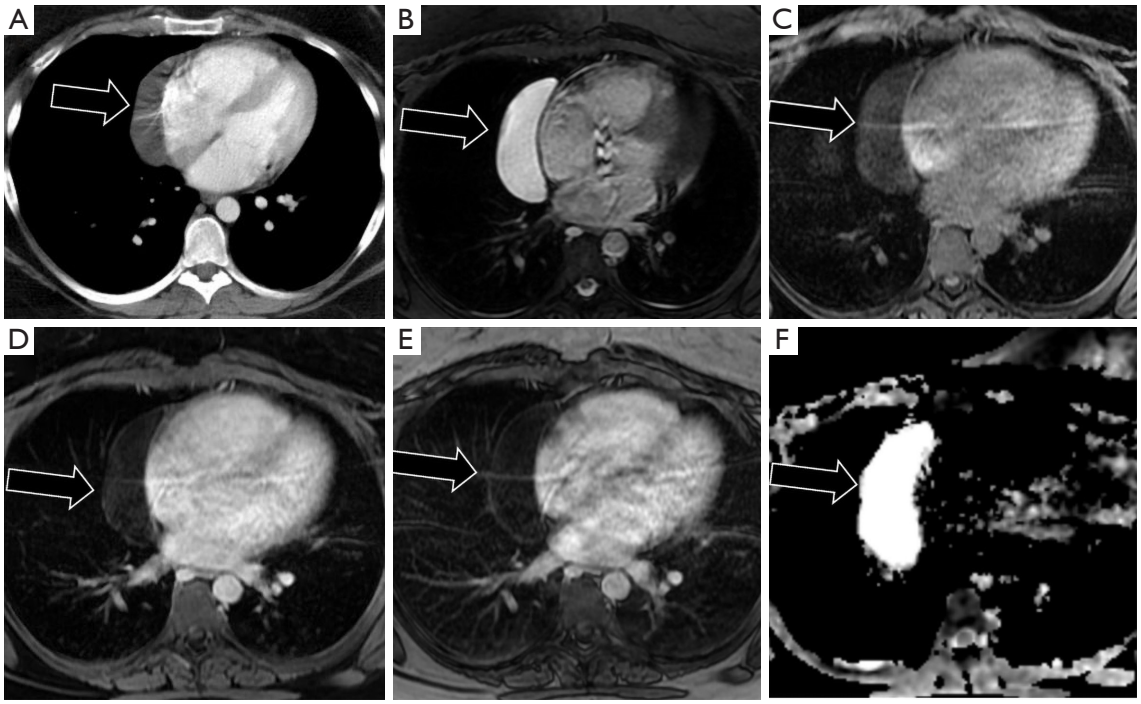

Figure 8 26-year-old female with pericardial cyst. CT imaging (black arrow) demonstrates a fluid density lesion along the right cardiac border (A), corresponding to T2W hyperintensity (B) and T1W hypointensity (C). The lesion does not demonstrate gadolinium enhancement (D), confirmed on delayed acquisitions (E). ADC maps demonstrate increased diffusivity (F). The location and imaging findings are confirmatory for pericardial cyst. CT, computed tomography; ADC, apparent diffusion coefficient.

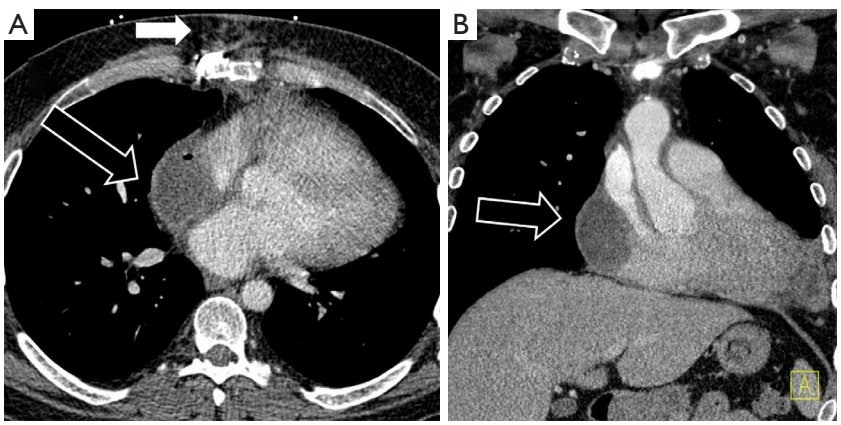

Figure 9 29-year-old male status post heart transplant with a pericardial abscess. Axial CT image after the administration of contrast demonstrated inflammatory changes in the sternum compatible with known infection (A, white arrow). A loculated pocket of fluid with small amount of gas is noted in the pericardium, immediately adjacent to the right atrium, compatible with intrapericardial abscess formation (A, black arrow; B, black arrow). CT, computed tomography.

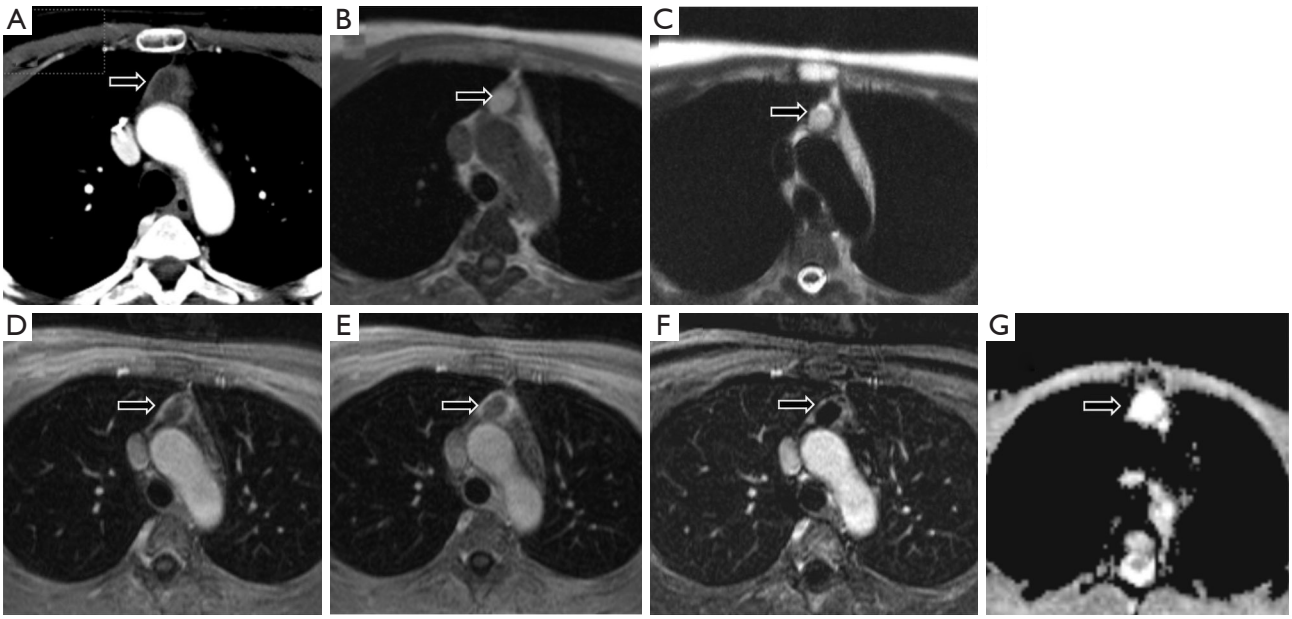

Figure 10 A 37-year-old male with negative tissue cultures but tissue PCR consistent with histoplasmosis. A contrast-enhanced CT demonstrates a thick walled, hypodense collection in the prevascular compartment (A, black arrow). MRI demonstrated (black arrow) a high T1 (B), high T2 (C) signal lesion with peripheral enhancement after the administration of gadolinium (D; delayed acquisition E). Subtraction images confirm the lack of internal enhancement (F). ADC images demonstrate increased diffusivity (G). PCR, polymerase chain reaction; CT, computed tomography; MRI, magnetic resonance imaging; ADC, apparent diffusion coefficient.

thecal sac confirms a diagnosis of meningocele (14).

Cystic schwannoma

Schwannomas are benign neoplasms arising from peripheral nerve sheaths. MRI is helpful in identifying the lesion and characterizing extension through the neuroforamen. Schwannomas are typically T2 hyperintense with small, ring-like hypointensities representing nerve fascicles. Schwannomas have a characteristic pattern of heterogenous contrast enhancement. Cystic degeneration leads to areas of very bright T2 signal (*Figure 11*). Contrast administration can help differentiate cystic degeneration of a Schwannoma from other cystic lesions, as the underlying Schwannoma will retain its heterogeneous enhancement pattern (14).

Neurenteric cyst

Neurenteric cysts represent a notochordal defect in which a persistent connection between the bowels and spinal canal is present. Most commonly in the posterior mediastinum, right hemithorax, and above the carina, these typically present as ventral paravertebral cysts with accompanying vertebral abnormalities, particularly of the thoracic spine. Signal characteristics are similar to meningocele (following CSF). If the connection to the bowel is patent, air or air-fluid levels may be seen (18).

Mullerian cyst (cysts of Hattori)

First characterized by Hattori in 2005, müllerian cysts are rare paravertebral cystic lesions in the T3–T8 region (19). Typically found in women aged 40–60 with concomitant gynecologic pathology, these lesions are thought to arise due to müllerianosis, a process by which müllerian tissues are developmentally misplaced (20). A cyst of Hattori is a singular, well-defined fluid attenuation lesion without enhancement that does not communicate with other structures, usually measuring less than 10 cm. Histopathologically, these lesions resemble fallopian tissue and display estrogen and progesterone receptor positivity. Surgical excision is often the preferred treatment given a presumed risk of malignant transformation (21).

Cyst-like lesions

Mediastinal pancreatic pseudocyst

A rare complication of acute and chronic pancreatitis is mediastinal extension of a pancreatic pseudocyst,

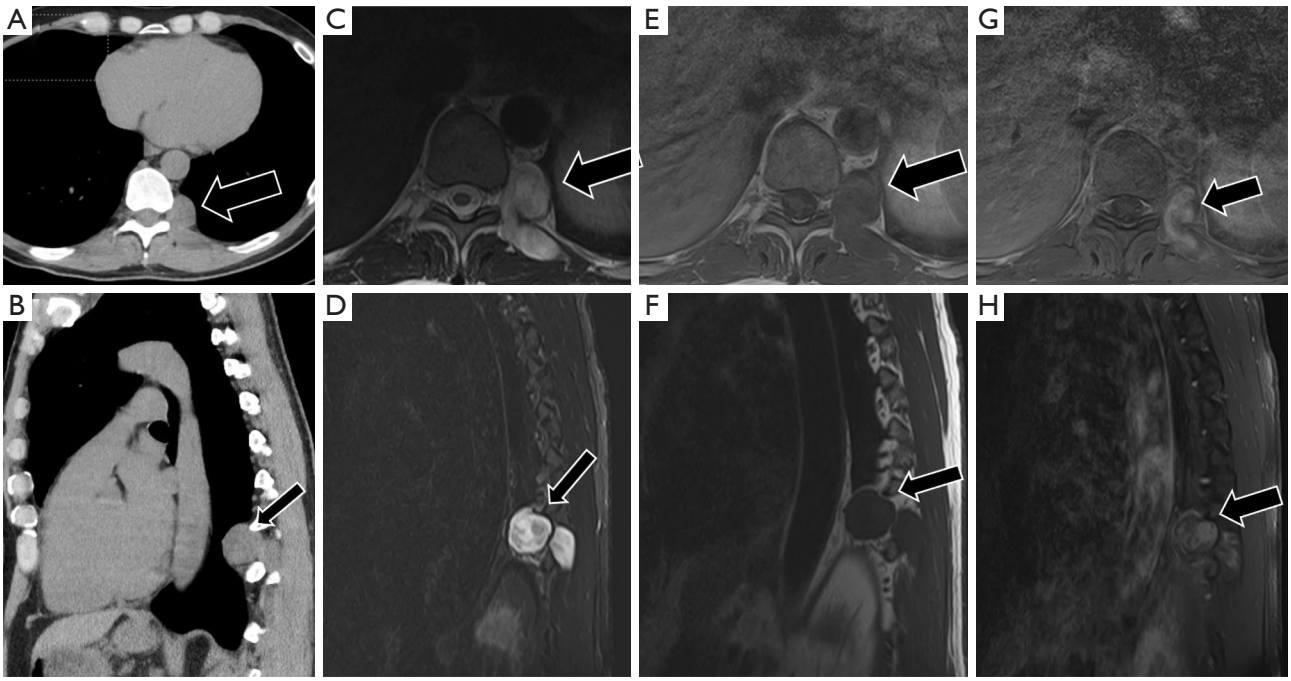

Figure 11 55-year-old male with cystic degeneration of a schwannoma. CT imaging demonstrates a soft-tissue density lesion (black arrow) arising in the paravertebral compartment (axial, A; sagittal, B). MRI imaging (black arrow) demonstrates a high T2 (axial, C; sagittal, D), intermediate T1 signal (axial, E; sagittal, F) lesion with extension to the posterior paraspinal musculature. Heterogeneous contrast enhancement is seen after the administration of gadolinium (axial, G; sagittal, H). Overall imaging findings compatible with cystic degeneration of a schwannoma. Also note the lack of direct communication with the thecal sac. CT, computed tomography; MRI, magnetic resonance imaging.

most commonly into the posterior mediastinum via the esophageal hiatus. Imaging characteristics will mirror those of abdominal pancreatic pseudocysts, typically thin-walled fluid collections, or alternatively, thick-walled, rim enhancing fluid collections. Communication with the abdominal cavity is typically, but not always, seen. Another potential route of communication and extension is a Morgagni hernia (congenital anterior diaphragmatic defect). Accurate diagnosis is critical as treatment for symptomatic lesions involves endoscopic-guided drainage with surgical resection necessary for most recurrent pseudocysts (22-26).

Ascending ascites via esophageal hiatus

Similar to pancreatic pseudocyst formation with mediastinal extension, intra-abdominal fluid contrast can ascend through the esophageal hiatus into the visceral mediastinum and simulate a cystic lesion (*Figure 12*). Fluctuation in shape and the presence of a concomitant sliding-type hiatal hernia help to confirm the diagnosis. Ascending ascites should follow the signal characteristics of the associated abdominal fluid and will not enhance.

Normal variants

Cysterna chyli

The cisterna chyli is a normal anatomical variant, representing a saccular dilatation of the retrocrural lymphatics as they ascend into the mediastinum. The cisterna chyli is often found immediately to the right of the aorta and can easily be mistaken for a cystic lesion. The characteristic location, morphology, and low attenuation on CT allow for confident identification (*Figure 13*). On MRI, the signal follows that of simple fluid (T1 hypointense, T2 hyperintense, no restriction).

Thymic hyperplasia

Thymic hyperplasia can be identified on CT imaging due to its characteristic location, triangular shape, and stippled appearance. However, in equivocal cases, in and opposed phase MR imaging can be used to demonstrate intracellular

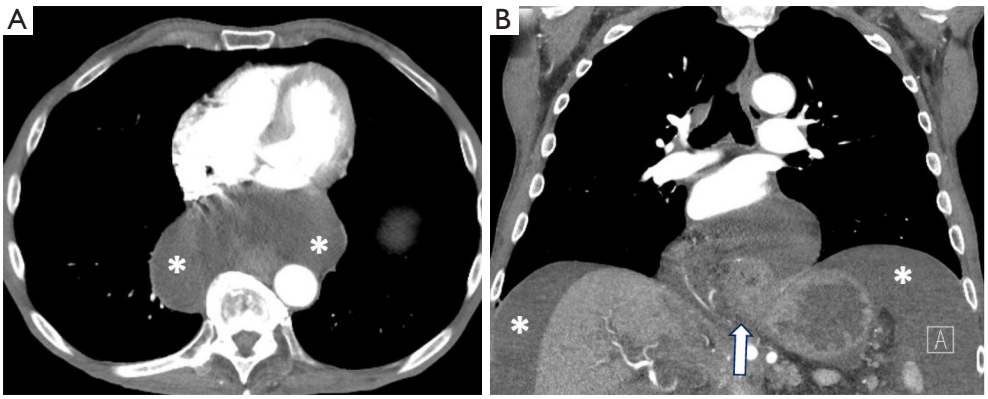

Figure 12 76-year-old male with ascending ascites. CT imaging demonstrates ill-defined hypoattenuation centered in the visceral compartment of the mediastinum (A, asterisks). No enhancement is present (A). Coronal image demonstrates the fluid is in continuity with abdominal ascites (B, asterisks). Note the hiatal hernia, a common finding in patients with ascending mediastinal ascites (B, white arrow). The hiatal hernia can also be faintly recognized in the selected axial image. CT, computed tomography.

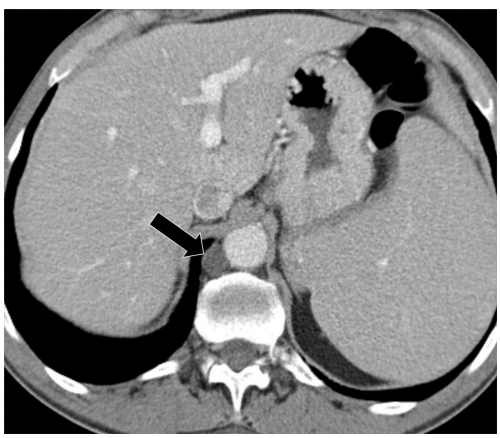

Figure 13 80-year-old male. CT image demonstrates a classic appearance of the cisterna chyli, a fluid-attenuation lesion located immediately to the right of the aorta at its diaphragmatic hiatus (black arrow). CT, computed tomography.

lipid, adding confidence to a diagnosis of thymic hyperplasia (12,27). One quantitative measure that may be used to differentiate benign from malignant prevascular (anterior) mediastinal thymic masses is the signal intensity index (SII), a ratio representing the percentage signal drop-off in out of phase imaging [(Thymus SI IP – Thymus SI OP)/ Thymus SI IP ×100%]. Values greater than 9%, typically 28–65%, were only seen in thymic hyperplasia (2,27,28). Another quantitative measure to differentiate benign versus malignant pre-vascular thymic lesions is the quantification of the chemical shift ratio (CSR) (27). A CSR ≤0.7 is consistent with normal or hyperplastic thymus, while a CSR ≥1.0 is indicative of thymic neoplasm in most cases (0.8 and 0.9 are indeterminate values). The formula to calculate CSR is as follows: CSR = OP SI thymus/OP SI paraspinal muscle/IP SI thymus/IP SI paraspinal muscle. Other studies have identified diffusion restriction as a predictor of malignancy, with some establishing quantitative ADC cutoffs that demonstrate 81% sensitivity. Lastly, contrast enhancement kinetics may be able to aid in differentiating low grade neoplasms from more aggressive lesions (2).

Thoracic duct cysts

Thoracic duct cysts can arise along its entire course, from the cisterna chyli to the supraclavicular region. Mediastinal thoracic duct cysts are extremely rare, accounting for only a few case reports in the literature (29). These lesions will follow signal characteristics similar to the cisterna chyli and lymphatic tissues, as above.

Pericardial recess

Fluid-filled pericardial recesses can be confused with mediastinal cystic lesions. Anatomical knowledge and imaging appearance of the pericardial recesses is needed to avoid confusion. Important pericardial recesses to mention include the posterior pericardial recess (blind ending extension of the oblique sinus) which is located immediately above the left atrium to the right of midline, and the pulmonary venous recesses which surround the pulmonary

veins near their attachment to the left atrium (30).

Conclusions

The imaging of cystic mediastinal lesions remains a diagnostic challenge. Location and imaging characteristics can often confirm a diagnosis without the need for tissue sampling. CT, MRI, and US each offer unique strengths and weaknesses. CT is often the first-line modality used in identification and characterization, MRI with T1 weighted pre and post contrast, T2 weighted, and diffusion-weighted sequences is a critical problem-solving tool, and ultrasonography useful in real-time characterization and procedural guidance. Findings suggestive of malignancy include enhancing solid or nodular components, thick vascular septations, and diffusion restriction. In equivocal or atypical cases, short-term follow-up imaging may be considered to reduce the number of unnecessary biopsies and/or resections.

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Footnote

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Case Report

Pyopericardium and extensive mediastinal abscess following EBUS-TBNA for mediastinal staging of NSCLC: a case report

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Background: Based on the algorithm on preoperative mediastinal staging in patients with non-small cell lung cancer (NSCLC), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is indicated in case of computed tomography (CT)-enlarged or positron emission tomography (PET)-positive mediastinal lymph nodes. It represents both a safe minimal invasive procedure with complication rates of less than 1.5% and a valid tool with a high sensitivity defining mediastinal nodal disease. However, infectious complications like mediastinitis or pyopericardium are most feared.

Case Description: A 54-year-old woman was admitted to our hospital for further investigation of a suspected NSCLC of the right upper lobe. EBUS-TBNA was performed to receive both diagnosis and samples of the mediastinal lymph nodes. Two weeks after EBUS-TBNA, the patient presented with symptoms of cardiogenic/septic shock: hypotension, tachycardia, chest pain and fever. Prompt diagnosis of concomitant infectious mediastinitis and extensive pyopericardium in consequence of EBUS-TBNA was obvious. Besides systemic antibiotics, bilateral thoracoscopic interventions finally made the breakthrough. The patient could be discharged roughly three weeks after emergent re-admittance. As being finally diagnosed with NSCLC (stage IIIA squamous cell carcinoma), the patient underwent—subsequent to induction chemotherapy—a definitive sequential chemoradiotherapy. Twelve-month follow-up confirmed stable disease.

Conclusions: It is to be expected that with increasing application of EBUS-TBNA as mediastinal staging tool, the number of serious infection-related complications will rise accordingly. The efficacy of antibiotic prophylaxis after EBUS-TBNA has not yet been proved and is therefore not included in any guideline. Our case gives an impression on the severity of delayed infectious complications after EBUS-TBNA and outlines up-front surgery as primary objective to broadly debride all contagious abscess-/empyema sites. With increased use of EBUS-TBNA as mediastinal staging tool, clinicians should be aware of this rare but highly critical peri-interventional complication in order to closely monitor endangered patients.

Keywords: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA); mediastinitis; pyopericardium; mediastinal lymph nodes; case report

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Introduction

A precise mediastinal staging for patients with potentially resectable non-small cell lung cancer (NSCLC) takes top priority, as it provides accurate evidence of tumor stage, guides the choice of treatment and predicts the patient's prognosis. Based on the algorithm for primary mediastinal staging, endosonographic tissue confirmation via endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is, inter alia, indicated in case of computed tomography (CT)-enlarged or positron emission tomography (PET)-positive mediastinal lymph nodes (1). It is true to the motto—"*apply diagnostic tools in increasing invasiveness*"—the first diagnostic choice for being both a safe minimal invasive procedure with complication rates of less than 1.5% and a valid tool with a high sensitivity defining mediastinal nodal disease (1-4). Among other peri-interventional complications—such as pneumothorax, pneumomediastinum and mediastinitis—a pyopericardium is a life-threatening condition and relativizes the apparent low complication rate in turn. If left untreated, it is rapidly progressive with mortality rates of up to 100% (5). Even when treated straight-forward, the mortality rate remain as high as 40%, mainly due to cardiac tamponade, constriction, and septic shock. With the increasingly widespread use of EBUS-TBNA, new questions arise on how to deal with such dreaded complications and—most important—how to prevent them. Focusing on this widely unknown foe, we report an impressive example of pyopericardium in conjunction with extensive mediastinal abscess following EBUS-TBNA for mediastinal staging of a NSCLC in the right upper lobe. We present the following case in accordance with the CARE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-22-13/rc).

Case presentation

A 54-year-old woman with a 6-week history of progressive dyspnea and productive cough presented with the radiologic suspicion of a lung carcinoma of the right upper lobe (*Figure 1A*,*1B*). Relevant secondary diagnosis was chronic obstructive pulmonary disease (COPD) GOLD grade 2 with excessive nicotine consumption (almost 80 pack years). Her medical history was otherwise unremarkable. In order to receive both diagnosis and rough mediastinal staging, EBUS-TBNA target structures were—besides airway mapping biopsies—lymph node stations 4R, 7 and 10R (*Figure 2A-2C*). Lymph node station 7 (size: 8 mm) was punctured once using a 22G Olympus needle, lymph node station 4R (size: 17 mm) was punctured multiple times as the received samples were constantly "crumbly", and lymph node station 10R (size 15 mm) was punctured in vain a multiple times. There was no bleeding or any other complication related to the procedure and the patient was discharged two days after the intervention with an unremarkable chest X-ray and normal laboratory findings without prophylactic antibiotics.

During the waiting period for histologic result, tumor board indicated PET-CT to rule out distant metastases. Unfortunately, as events turned out differently, the patient was readmitted exactly two weeks after EBUS-TBNA with symptoms of cardiogenic/septic shock: hypotension [Riva-Rocci (RR) 70/50 mmHg], tachycardia (140 beats

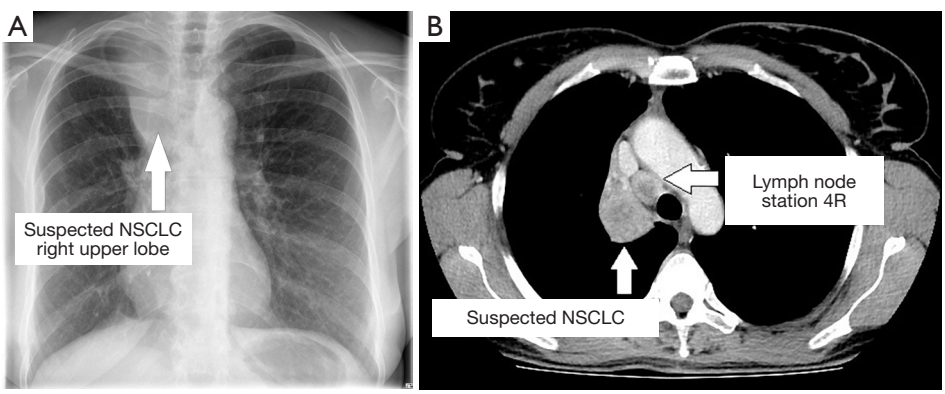

Figure 1 Both preoperative chest X-ray (A) and axial CT-scan with IV contrast (soft tissue window, B) implicates a NSCLC of the right upper lobe with tumor-positive lymph node station 4R (provisional TNM classification: T2 N2 Mx). NSCLC, non-small cell lung cancer; CT, computed tomography; IV, intravenous; TNM, tumor node metastasis.

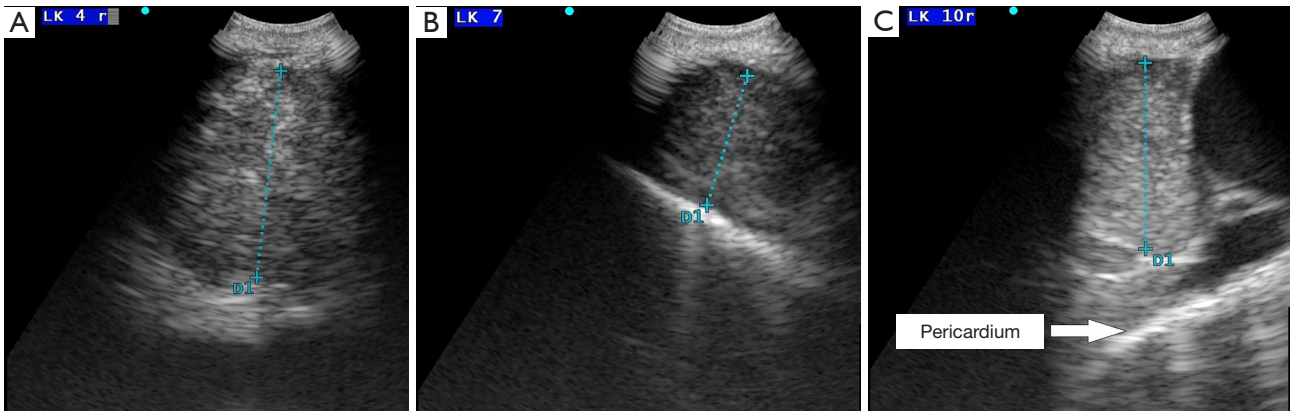

Figure 2 EBUS-TBNA of mediastinal lymph node stations 4R (A), 7 (B), and 10R (C). LK, lymph node station; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

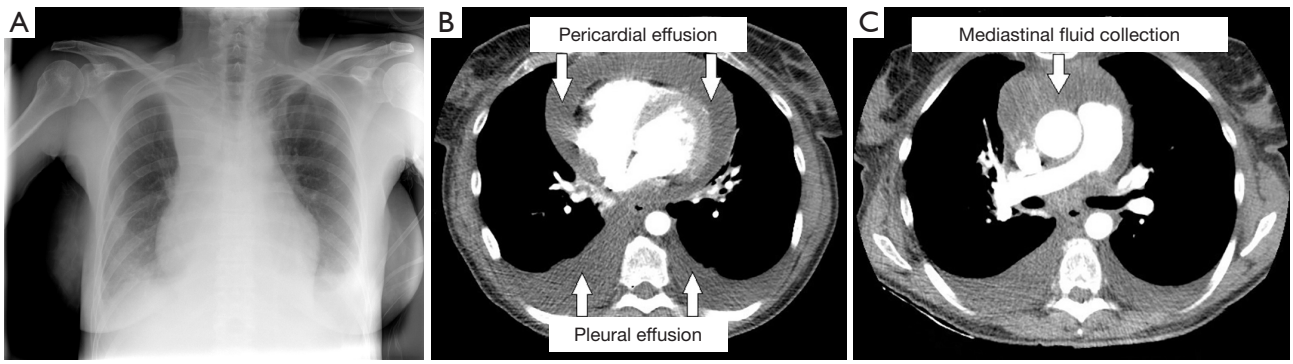

Figure 3 Two weeks after EBUS-TBNA, chest X-ray indicated massive pericardial effusion and concomitant heart failure (A). Axial CT-scan with IV contrast (soft tissue window) showed protein-rich pericardial effusion (B) and an organized mediastinal fluid collection (C), indicating a complicated pericardial effusion with possible mediastinal abscess formation. Additional pleural effusion reflected functional heart failure. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; CT, computed tomography; IV, intravenous.

per minute), tachypnea (35 breaths per minute), SpO_2 84% without oxygen supply, chest pain and fever (39 ℃). Electrocardiogram showed low voltage and ST-segment elevation in a wide range of leads. As already presumed in chest X-ray (*Figure 3A*), echocardiography revealed a circumferential pericardial effusion (size 2.5 cm) with tamponade physiology. CT-scan confirmed circular pericardial effusion with an intensity scale of 27 Hounsfield units (HU), indicating a complicated protein-rich effusion (*Figure 3B*). In addition, a thereof separate liquid formation in the anterior mediastinum with an extension of 69×21×37 mm (intensity scale 21 HU) pointed out a possible mediastinal abscess (*Figure 3C*). Laboratory results were as follows: white blood cells 30.2×10^3/μL (cut-off <11.3×10^3/μL), C-reactive protein level 149.5 mg/L (cut-off <10 mg/L), and procalcitonin level 1.44 ng/mL (cut-off <0.5 ng/mL).

With broad-spectrum antibiotics (piperacillin-tazobactam and clindamycin), the patient underwent urgent left-sided thoracoscopic pericardial fenestration and mediastinal abscess drainage (*Figure 4*). Even though postoperative catecholamine dose could be initially reduced, persistent tachycardia (120 beats per minute) prompted an echocardiographic control, which revealed a relevant residual pericardial effusion in the area around right atrium and ventricle. In addition, CT-monitoring showed a still detectable mediastinal fluid collection as with a possible persistent abscess formation (*Figure 5*). Clindamycin was

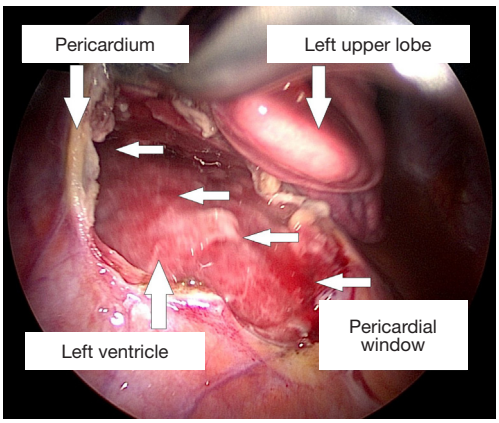

Figure 4 Intraoperative finding after evacuation of at least 300 mL opaque pericardial effusion and pericardial fenestration via left-sided video-assisted thoracoscopy.

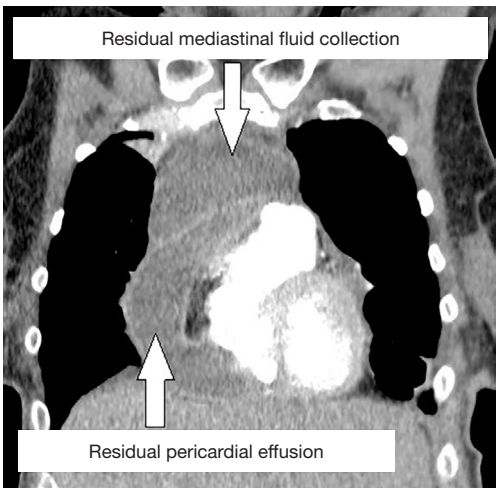

Figure 5 Interim coronal CT-scan with IV contrast (soft tissue window) displaying both residual pericardial effusion and residual mediastinal fluid collection as a possible indication for persistent abscess formation. CT, computed tomography; IV, intravenous.

replaced by linezolid. Subsequent right-sided thoracoscopic pericardial fenestration and residual mediastinal abscess drainage was unavoidable seven days after the initial intervention. Renewed rise in infectious blood values was expression of residual purulent effusion in the right-sided pleura not being drained via the inserted chest tubes. Re-thoracoscopy for fluid discharge and further adjustment of antibiotics (linezolid replaced by meropenem) rounded the therapy off.

Even though cultures from various pericardial/mediastinal fluid probes remained inconspicuous, surgical intervention and antibiotic therapy were finally a breakthrough: both cardiac function and laboratory findings recovered. Meanwhile, histologic examination of the mediastinal lymph nodes revealed necrotic material with squamous cell carcinoma in lymph node station 4R. As the final chest drainage was removed 20 days after the initial operation, the patient could be discharged on day 23 after readmission.

In the successive oncologic course, PET-CT could substantiate the initial suspicion of a stage IIIA NSCLC (T2 N2 M0). To precisely determine mediastinal nodal status, video-assisted mediastinal lymphadenectomy (VAMLA) confirmed tumor-positive lymph node station 4R with extranodal extension (ENE+) and tracheal penetration. Subsequent to induction chemotherapy, the patient underwent definitive sequential chemoradiotherapy. Twelve-month follow-up confirmed stable disease.

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 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.

Discussion

The value of EBUS-TBNA as minimally invasive technique for mediastinal staging of NSCLC is undisputed. The risk-benefit ratio is in high favor of the procedure, but the pendulum gets out of balance when out of an approximately 1% risk of complication a specific patient suffers a 100% disaster with a potentially fatal course.

Etiology and beneficial risk factors for infectious complications are easy to comprehend. When the bronchoscope passes the oropharynx, it might get contaminated with oropharyngeal bacteria such as *Streptococcus*, *Staphylococcus*, *Coryneform bacteria*, *Prevotella melaninogenica*, *Actinomyces odontolyticus*, and *Eikenella corrodens*, inter alia (6). The aspiration needle picks up the pathogens either along its passage through the bronchoscope's working channel or within the airway following removal of its open-ended plastic sheath during use (7). The as of now contaminated aspiration needle inoculates the oropharyngeal bacteria into the mediastinal tissue being biopsied (2,7,8). It is therefore important to

note that aspirating airway secretions via the bronchoscope prior to insertion of the needle sheath will increase the risk of working channel contamination (9). But sole contamination of the bronchoscope does not seem to be the key explanation as both numbers of EBUS-TBNA interventions and numbers of documented EBUS-TBNA-associated infectious complications are diametrically opposed. It's rather understood as prerequisite for additional risk factors.

Potential risk factor for peri-interventional mediastinitis is the puncture of necrotic or cystic structures (2,8,10). Due to the avascular environment and hence unavailable immune system of necrotic lesions or cysts, inoculation of bacteria into these structures might lead to locally uninhibited bacterial growth (7,11). It is assumed that the risk for infection is increased three-fold when necrotic lesions are biopsied (2). Against this backdrop it is advisable to thoroughly examine the chest CT-scan pre-interventionally to avoid biopsies of necrotic lesions whenever possible. If biopsies are still essential, however, both the number of times the needle punctures the lesion and the number of samples obtained per lesion should be limited (12). Associated further risk factor for contagious spread is the skill of the interventionalist.

As for the formation of mediastinitis, main risk factor for the development of a pyopericardium is linked to the act of puncture. When the aspiration needle is used in its entire extension, the pericardium might get unintentionally damaged with subsequent aspiration of the pericardial recess (7). It requires experience to unequivocally differentiate the pericardial recess from a lymph node (13). Our very skilled interventionalist targeted each of the biopsied lymph nodes with a suitable needle penetration depth, hence maintaining a safe distance from the pericardium. Retrospectively, there are two observations. First, one target structure of EBUS-TBNA was lymph node station 4R, which is the lower paratracheal lymph node on the right and located close to the superior pericardial recess. Lymph node station 4R contained a bulky necrotic lesion, and even though no direct inoculation of the pericardium is assumed to have occurred, contiguous spread might have developed by simple tissue prick of the adjacent pericardium (13). Second, the pericardium could be easily displayed while exploring lymph node station 10R, which is the hilar lymph node zone. Displaying vital structures timely ahead any attempt of taking tissue samples should become an indispensable reflex of any interventionalist.

Even though the onset of mediastinitis and/or pyopericardium is variable, most cases occurred within three weeks (median time 12.5 days) after EBUS-TBNA (12,14,15). Only one study reports a delayed onset in two patients, in whom mediastinitis occurred 40 and 53 days following EBUS-TBNA (15). Despite this exception, the patients should be thoroughly monitored for infectious complications in-between a two-week interval after the intervention. Reflecting our case, if our patient would have been sensitized to possible symptoms or would have been given the vivid advice of urgent in-hospital visit in case of discomfort, the situation would have possibly been recognized at least 5 days earlier. But some patients understate their physical condition—making any precaution futile.

The only curative treatment option is up-front surgery. Even if doing so, it feels like chasing after clinical findings—as our case strikingly shows. Although lagging behind, surgery is the savior. All the more as—not unusual—the underlying organism could not be identified on culture (16). Our patient needed three operations in the end to finally get a full debridement of all purulent cavities. The focus is on quick identification of crucial symptoms and rapid therapeutic decision-making.

Can we prevent the event of an infectious complication after EBUS-TBNA by prophylactic administration of antibiotics? Up to now no study on this focus showed any real benefit of prophylactic antibiotics in immunocompetent patients—not to mention subtleties like optimal start and duration of antibiotic treatment or the number needed to treat to prevent a peri-interventional infection (4,7). A transparent explanation for this observation is that antibiotics lack to penetrate into avascular structures such as large necrotic lymph nodes. Consequently, no international guideline—for example (I) the American Association of Bronchology and Interventional Pulmonology, (II) the American Association for Thoracic Surgery, (III) the American College of Chest Physicians, (IV) the Canadian Thoracic Society, (V) the European Association for Bronchology and Interventional Pulmonology, and (VI) the Society of Thoracic Surgeons—recommends the use of prophylactic antibiotics following EBUS-TBNA (17). Apart from patients with prosthetic heart valves, history of endocarditis, or asplenia, the prophylactic administration of peri-interventional antibiotics does rather seem to ease ones conscience than being based on evidence-based medicine (13). Another aspect is a sufficient oral hygiene before the procedure to decrease the amount of oral

cavity pathogens and hence decrease the risk of infection (18). To achieve this, a possible supplementary starting point is a mouth rinse or full mouth disinfection before the procedure (9). A conceivable prospective approach in high risk patients (i.e., immunocompromised patients due to diabetes, medical treatment or being transplanted) might be—despite being not evidence-based—the combination of pre-interventional mouth rinse and peri-interventional prophylactic antibiotics (4).

Inconspicuous side effect of peri-interventional infectious complications is that nearly 20% of these patients did not underwent essential anti-cancer treatment as their general condition permits it due to prolonged therapy for infectious complications (2). Our patient—as finally being diagnosed with stage IIIA NSCLC—was suitable for curative treatment and received definitive chemoradiotherapy. Even though a delay in initiating anti-cancer treatment was recorded (interval of EBUS-TBNA to therapy), its oncologic significance remains to be seen.

Our case reports a prime example of its genres limitations. It represents a single observation and does not allow any smooth conclusions. However, it may have educational value and could help improve peri-interventional practice as it illustrates a relevant and challenging case. The complication reported represents an adverse peri-interventional event—one that surgeons refer to as *happily not me* instead of pointing fingers at anyone—that occurred but (at least) did not lead to patient's permanent harm. Comprehensive reporting of potential peri-interventional complications remains a fundamental element in endoscopic interventions. Ongoing investigation of the patients' phenotype with infectious complications after EBUS-TBNA may uncover possible causes and hence be useful for patients in need for selective prophylactic antibiotic treatment.

Recapitulating possible current strategies to prevent infectious complications after EBUS-TBNA—or at least reduce their impact: (I) pay special attention to possible necrotic texture of the designated target lesions on CT-scan; (II) strictly adhere to recommended guidelines for equipment decontamination; (III) ensure an adequate oral hygiene prior to EBUS-TBNA; (IV) guarantee a clear ultrasound vision of the puncture site; (V) limit the number of punctures; (VI) avoid biopsies of necrotic and cystic lesions; (VII) carefully monitor the patient post-interventionally to detect infectious complications as quick as possible.

Summarizing her reflections of in-hospital stay, closing remarks are from our patient: "Following my diagnosis of lung cancer I was understandably depressed. During in-hospital stay for interventional bronchoscopy, I was told that there might be effective treatment options whatsoever the extent of the tumor will be. That gave me confidence. As my physical condition worsened in the waiting period for further diagnostics, I was cautious to go hastily to hospital again due to the ongoing COVID-19 pandemic. Ultimately, with increasing deterioration my readmission was indispensably required. Never felt worse in my entire life. After the first operation I felt better, but the necessity of additional operations made me hopeless at first. I feared not to survive—but I am a fighter. In the end all worked out: it went uphill after the third operation and I fully recovered. Surgery finally saved my life. In retrospect, I was surprised how quick I convalesced. True to the motto "*once I achieve this*, *I can achieve everything*" I began chemoradiotherapy with confidence. In hindsight, I should have gone much earlier to hospital. I'm pretty sure the course of the disease would have been different".

Conclusions

EBUS-TBNA is a well-established and valid mediastinal staging tool. With its increasing application, associated complications like infectious events are accumulating. Even though still rare, rapid diagnosis and quick surgical treatment is of utmost importance to avoid fatal outcome. As international guidelines do not recommend peri-interventional prophylactic antibiotic therapy, a thorough post-interventional monitoring of patients is an indispensable requirement.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-22-13/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-22-13/coif). The authors have no conflicts of interest to declare.

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 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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Case Report

Good's syndrome and COVID-19: case report and literature review

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Background: Good's syndrome (GS) is an adult-onset acquired immunodeficiency, in which patients present with thymoma and hypogammaglobulinemia (HGG). GS is characterized by low to absent peripheral B cells and impaired T-cell mediated immunity, often resulting in various (opportunistic) infections and concurrent autoimmune disorders. In this case report, we present a case of a patient with GS and coronavirus disease 2019 (COVID-19) infection after surgical removal of a thymoma. The simultaneous occurence of these two entities is extremely rare.

Case Description: A 55-year-old man presented with oral lichen planus and cutaneous lesions. Additional symptoms included a weight loss of 5 kilograms in the last six months. Computed tomography (CT) and positron emission tomography (PET) of the chest showed a large anterior mediastinal mass with a maximum diameter of 10 centimetres. A core needle biopsy was performed, which led to a pathological diagnosis of thymoma type AB. In addition to these earlier findings, laboratory analysis revealed HGG. The combination of a thymoma and HGG led to a diagnosis of GS. Induction chemotherapy with cisplatin-etoposide was started, however, the patient developed COVID-19 after 2 cycles. Treatment with remdesivir was initiated and, subsequently, a thymectomy via sternotomy was performed. Final pathology confirmed a thymoma type AB of 14 centimetres, fully encapsulated, and without invasion. Resection margins were negative and the tumour was classified as pT1aN0, R0 resection. The patient has received immunoglobulin treatments every 4 weeks for his GS and has not developed any new infections since the start of this therapy.

Conclusions: Patients with GS are prone to developing (pulmonary) infections. Clinicians should be aware of the possible clinical effects of COVID-19 infections in this patient population.

Keywords: Coronavirus disease 2019 (COVID-19); Good's syndrome (GS); hypogammaglobulinemia (HGG); thymoma; case report

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Introduction

Good's syndrome (GS) is a rare adult-onset acquired immunodeficiency that involves thymoma, hypogammaglobulinemia (HGG), and a significantly reduced or absence of peripheral B cells (1). The incidence rate of GS is estimated to be 1.5 per 1,000,000. GS was first described in 1954 by Robert Good as a rare association between thymoma, invasive bacterial infections, and HGG, often occurring between the fourth and sixth decades of life (2). Despite the fact that GS has been known for over sixty years, the exact pathophysiology is still unclear. The majority of data on GS is from case reports or small case series, making it difficult to investigate the underlying pathogenesis of the disease. Nevertheless, research in recent years have elucidated several aspects of GS and have clarified some previously held misunderstandings regarding its immunopathology. Initially, researchers suggested that GS was a subset of common variable immunodeficiency (CVID) due to similar patterns of occurrence of invasive

bacterial and opportunistic infections. Despite similarities in clinical presentation, the underlying genetic backgrounds and immune pathologies differ (3). Studies have found no conclusive evidence for disease-causing genetic variants associated with GS. Until now, only three genetic studies have been conducted, including a total of eight patients. Two of these patients were reported to have a mutation in transmembrane activator and CAML interactor (TACI), and one patient had two missense mutations in B-cell activating factor receptor (BAFF-R). Both of these genes are members of the tumour necrosis factor receptor (TNFR) superfamily and are involved with the maturation and homeostasis of B cells. In CVID, monogenic defects are present in some patients, and variants of the previously mentioned genes have also been associated with CVID (4-6). The majority of CVID patients have normal to moderate levels of B cells, but with defects in peripheral B cell differentiation, survival and antibody production. In GS, patients generally lack B cells, which is more similar to patients with agammaglobulinemia, and suggests a defect in lymphopoiesis during the early B cell development (2).

The disease presentation of GS is variable and recognition of GS across a range of clinical manifestations is challenging, often leading to diagnostic delay. Recurrent bacterial infections, increased rates of opportunistic infections such as Pneumocystis jirovecii, mucocutaneous candidiasis, and reactivation of latent viruses such as herpes simplex virus and varicella zoster are one of the main clinical features of GS (7). Thymoma is also one of the main clinical features of GS, and is often found incidentally during workup for a suspected myasthenia gravis (MG) or in patients investigated for recurrent pulmonary infections. The majority of thymomas in GS are benign and localized. Thymectomy has not been shown to improve HGG in patients with GS, indicating that thymoma management alone is not sufficient as treatment (2). Treatment for GS is mainly supportive and includes antimicrobials and immunoglobulin replacement. Infections remain one of the leading causes of mortality in GS and the prognosis is believed to be worse compared to other adult immunodeficiencies (8). In the last two years, coronavirus disease 2019 (COVID-19) has shown to have higher morbidity and mortality rates in patients with primary and secondary immunodeficiencies compared to the general population (1). However, there is a paucity of data regarding the susceptibility to COVID-19 patients and the clinical outcomes of COVID-19 in patients with GS. In this case report, we describe a patient who presented with GS and a simultaneous COVID-19 infection. Details of the case and a review of the latest data on GS are presented. We present the following case in accordance with the CARE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-22-12/rc).

Case presentation

A 53-year-old man presented to the department of dermatology with symptoms of oral lichen planus and a papular erythematous rash on chest and arms. The patient had previously been treated with 2 courses of methylprednisolone at a maximum of 32 mg/day, which was slowly tapered to a maintenance dose of 2 mg every 2 days. However, the patient's symptoms recurred both times after lowering the dose below 4 mg/day. Additional symptoms included a weight loss of 5 kilograms in the last six months. The patient had no relevant medical or family history. Initially, the patient had been treated with corticosteroids and hydroxychloroquine. However, the patient noticed that the symptoms returned after several attempts to stop with the initial corticosteroids treatment. For this reason, the treatment regimen was changed to acitretin, a second generation retinoid.

Work-up with laboratory tests and a chest X-ray were performed, with the latter showing evidence of lymphadenopathy (not shown). Subsequent computed tomography (CT) and positron emission tomography (PET) of the chest showed a large anterior mediastinal mass with a maximum diameter of 10 centimetres (*Figure 1A*,*1B* and *Figure 2*). A core needle biopsy was performed, which showed spindle-shaped cells and lymphoid cells. Additional tests showed terminal deoxynucleotidyl transferase (TdT), cluster of differentiation 3 (CD3), and CD5 positivity in the lymphoid cells. Furthermore, pancytokeratin (CKpan) was positive in the spindle-shaped cells. This led to a pathological diagnosis of a thymoma type AB. Furthermore, flow cytometry showed a low B-cell count and $CD4^+/CD8^+$ ratio (*Table 1*). Acetylcholine receptor antibodies were not present.

In addition to these findings, laboratory analysis revealed HGG (*Table 2*). The combination of a thymoma and HGG led to a diagnosis of GS for which treatment with immunoglobulin therapy was initiated at a dose of 25 grams every 4 weeks. Due to the volume of the mass and the close relation with major cardiac and pulmonary vessels, a multidisciplinary decision was made to administer induction chemotherapy with cisplatin-etoposide prior to surgery. After 2 cycles, the patient developed a cough, loss of taste

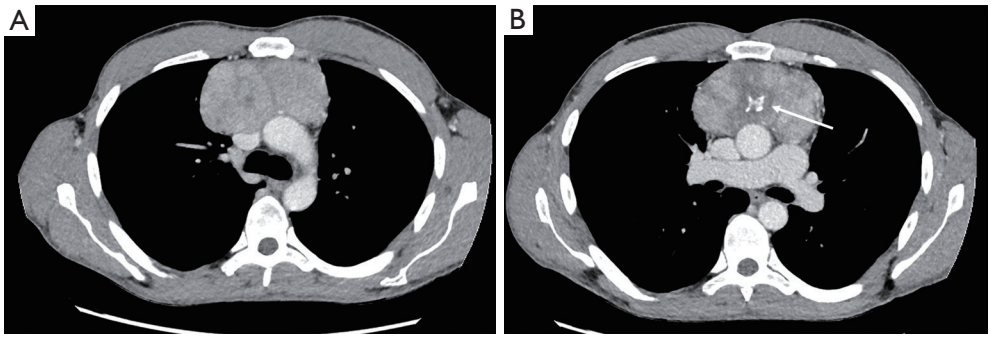

Figure 1 Axial contrast-enhanced chest CT images showing a large mass in the prevascular mediastinal compartment. (A) The tumour is lobulated and well-defined, and (B) has a heterogeneous aspect, with low-density areas corresponding with necrosis as well as an area of chunky calcifications (white arrow). CT, computed tomography.

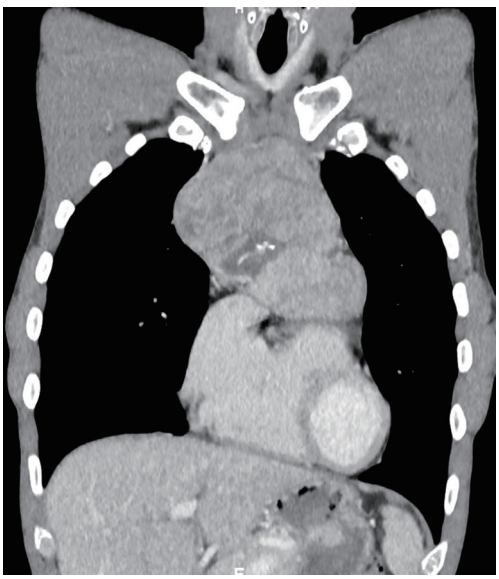

Figure 2 Coronal reformatted contrast-enhanced image clearly depicts the large extend of the mass, as well as the heterogeneous aspect.

Table 1 Flow cytometry showing absence of B-cells and a reduced $CD4^+/CD8^+$ ratio

Cell population	Value	Normal range	Unit
T cell: CD3	778	700–2,100	cells/μL
T helper cells: $CD4^+/CD3^+$	240	300–1,400	cells/μL
$CD4^+/CD8^+$ ratio	0.49	1–3.6	–
B cell: CD19	<6	100–500	cells/μL

CD, cluster of differentiation.

Table 2 Laboratory analysis of immunoglobulin levels

Immunoglobulin	Value (g/L)	Normal range (g/L)
IgG (turbidimetric)	2.45	6.5–16
IgA (turbidimetric)	<0.15	0.4–3.5
IgA (nephelometric)	0.12	0.7–4.0

IgG, immunoglobulin G; IgA, Immunoglobulin A.

and smell, dyspnoea, and fatigue. He was admitted to the hospital and was diagnosed with COVID-19. Initially, the patient was subfebrile, however, he developed a fever (39.8 ℃) within 4 days. Oxygen therapy at 2 L/min was initiated due to low blood oxygen saturations. The patient was discharged in a stable condition after two weeks.

Six weeks after the initial PET-CT, a new chest CT-scan showed no evidence of volume reduction. Despite the fact that there was no volume reduction, a multidisciplinary decision was made to perform a surgical resection of the mass via sternotomy. However, screening for COVID-19 at time of admission was positive, despite absence of any symptoms. Due to the patient's prolonged COVD-19 viral shedding, the immunocompromised state, and the absence of COVID-19 seroconversion (no COVID-19 immunoglobulins on serology), treatment with remdesivir, a broad-spectrum antiviral therapy, was initiated according to the national guidelines at that time. After one week of treatment, a thymectomy via sternotomy was performed. Final pathology confirmed a thymoma type AB, fully encapsulated, without signs of invasion, and with a maximum diameter of 14 centimetres. Resection margins were negative and the tumour was classified as pT1aR0.

Due to persistent COVID-19 shedding in the postoperative period, convalescent plasma was administered. However, this did not have any effect on the asymptomatic COVID-19 shedding. The patient was discharged in excellent condition. The patient received two doses of an mRNA vaccination 14 weeks after his discharge. However, even after vaccination, the COVID-19 shedding continued, which indicates that the patient is a vaccine non-responder. Since then, the patient has received immunoglobulin treatments at a dose of 350–400 mg/kg every 4 weeks for his GS and has not developed any new infections since the start of this therapy. 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 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.

Discussion

Current evidence suggests that GS is a secondary immunodeficiency that is induced by thymic tumours. In a systematic review by Kelesidis *et al.*, invasive spindle cell thymomas were the most common type associated with GS (9). However, in a retrospective survey by Zaman *et al.*, 59% of patients with GS had AB as histological type of tumour (10). Current data suggests that the time of diagnosis of the thymoma often differs between patients; the thymoma diagnosis can precede, occur concurrently, or follow the diagnosis of HGG (2). In the study by Zaman *et al.*, the median age of GS diagnosis was 58 years (range, 51–62 years) with a median interval of four years between the diagnosis of the thymoma and HGG. Previous studies have not shown any significant effects of thymectomy on the immunological symptoms of these patients (2,9). This has led some authors to believe that thymomas are more likely to be a clinical result than the driving factor behind the B cell depletion in GS patients. Nevertheless, a number of studies have shown that the thymic tumour microenvironment can cause an aberrant maturation of T cell precursors, leading to an altered T cell subset in the blood. However, the majority of data is derived from studies regarding MG (11-13).

No genetic defects in B cell differentiation have yet been identified in patients with GS, which suggests that there may be some intrinsic and/or extrinsic factors driving the B cell lymphopenia. In a study by Masci *et al.*, an oligoclonal expansion of a subset of CD8 T cells with a vβ8 T cell receptor was found in the bone marrow of patients with thymoma and B cell lymphopenia. However, this subset expansion was not demonstrated in the same patients' peripheral blood lymphocyte population. Further analyses using genetic sequencing revealed that this could be an antigen-specific response to a previously unknown pathogen or an autoimmune reaction towards B cell progenitors (14). Some authors have hypothesized that the development of the autoimmune response in GS patients could be multi-factorial as well. A number of viruses and bacteria have been postulated to cause auto-immunity through epitope spreading, molecular mimicry, and cross-reactive antibody production. No pathogenic agent has yet been identified (15).

Regarding the possible association between a COVID-19 infection and GS, only a few cases have been published. There is controversy regarding the way in which patients with antibody deficiencies react to COVID-19. Some authors have even suggested that the intrinsic lack of B cells could be considered an advantage in COVID-19 by preventing the development of a hyper inflammation state (16). Several case studies of patients with agammaglobulinemia showed that, paradoxically, patients with B cell deficiencies showed milder courses of disease and did not require mechanical ventilation (17-19). In our patient, the COVID-19 infection was not severe and conservative measures proved to be sufficient. Nevertheless, our patient did demonstrate prolonged COVID-19 shedding 14 weeks postoperatively, even after two doses of mRNA vaccinations. Regular administration of immunoglobulin replacement therapy has resulted in a stable condition without any new signs of infection. More data regarding the aetiology and underlying immunopathology are necessary to fully understand GS and to create better treatment options. Furthermore, more data on the clinical outcomes of COVID-19 infections in GS patients is needed to see whether this patient population is more prone to develop severe outcomes than the general population.

Patient perspective

Our patient mentioned that the first weeks after his diagnosis were quite stressful, mainly due to the uncertainty regarding his diagnosis and the treatment plan. The numerous visits to the hospital put quite a lot of strain on our patient, keeping in mind that he had no relevant medical history prior to his new diagnosis of GS. The fear of the effects of the COVID-19 infection further increased

the patients worries regarding his health. However, following the successful operation and improvement of his clinical symptoms, our patient reported to be less stressed about his (future) health status.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-22-12/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-22-12/coif). The authors have no conflicts of interest to declare.

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 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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Case Report

Extensive fibrosis in mediastinal seminoma is a diagnostic pitfall in small biopsies: two case reports

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Background: In mediastinal biopsies that show fibrosis, the differential diagnosis includes fibrosing mediastinitis, immunoglobulin G subclass 4-related disease, Hodgkin lymphoma, as well as reactive fibrotic and inflammatory changes adjacent to other processes including neoplasms.

Cases Description: We report two cases of incidentally detected mediastinal seminoma that contained extensive areas of paucicellular fibrosis, which precluded accurate preoperative biopsy diagnosis. The fibrosis consisted of mildly inflamed, densely scarred tissue with thin dilated vessels, and was present to a significant extent that is suggestive of spontaneous regression. These features are not currently described in the World Health Organization Classification of Thoracic Tumors. In both patients, needle and open biopsies sampled only the fibrotic areas of the tumors, and the final diagnosis was not achieved until surgical excision was performed. After surgery, both patients received chemotherapy, and were alive without evidence of disease at 3.4 years and 1 year post-operatively, respectively. Tumor fibrosis composed approximately 95% and 50% of each patient's tumor, respectively. In one of the patients, correlation of the needle biopsy position with the positron emission tomography (PET) scan revealed that the biopsy needle had sampled a non-metabolically active portion of the tumor.

Conclusions: While pathologic spontaneous regression is well-described in gonadal germ cell tumors, it is not well-reported in extragonadal locations. Prospective knowledge of this diagnostic pitfall and targeting PET-avid regions of the tumor may increase the diagnostic yield and help to avoid non-indicated surgical interventions.

Keywords: Mediastinal; seminoma; regression; case report

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Introduction

The mediastinum can be affected by many different types of tumors and inflammatory conditions, with differing therapeutic options. Therefore, the work-up of an anterior/prevascular mediastinal mass includes clinical, laboratory (serum β-human chorionic gonadotropin (β-hCG), alpha fetal protein (AFP), lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), and autoantibodies against acetylcholine receptors), and imaging studies to hone the differential diagnosis and clarify the extent of disease. Primary mediastinal seminomas, while rare, are the

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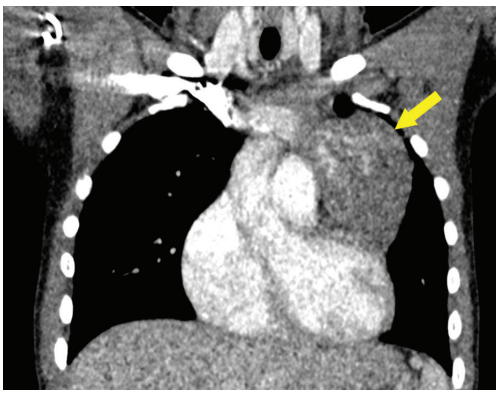

Figure 1 Case 1 imaging. Coronal contrast-enhanced pediatric protocol low dose CT showed a left prevascular mediastinal mass (arrow) that is well-circumscribed, and lobulated, with serpiginous heterogeneous enhancement. CT, computed tomography.

second most common (10–37%) primary germ cell tumor of the mediastinum, behind teratomas. Mediastinal seminoma occurs almost exclusively in young men, more frequently in the second and fourth decades (range, 9 to 79 years old) (1). Most patients are asymptomatic, with incidental discovery of a large mediastinal mass (1). Their serum markers are frequently within normal limits, although mildly elevated β-hCG and LDH levels have been reported. On imaging studies, mediastinal seminoma usually presents as a large and homogeneous mass with mild enhancement on contrast-enhanced computed tomography (CT) (2), which is radiographically nonspecific. Therefore, tissue sampling, most often by core needle or fine needle aspiration biopsy, is necessary for diagnosis. The most commonly recommended management of patients with seminoma is systemic platinum-based chemotherapy, or radiation for localized disease if chemotherapy is contraindicated. Surgery may be considered as salvage therapy, but is not recommended as the primary modality of therapy, unless the tumor is very small and localized (3-6).

Here we report two cases in which preoperative clinical evaluation and biopsies failed to render a specific diagnosis of primary mediastinal seminoma, leading to surgical excision. Pathologic examination of both resected tumors revealed extensive areas of fibrosis suggestive of spontaneous tumor regression. Tumor regression is not well-defined, and there is no standard for grading regression. Some have proposed scoring tumor regression by comparing the volume of viable tumor cells to the volume of fibrosis (7). Fibrous septa/stroma is mentioned in the morphologic description of primary mediastinal seminoma in the World Health Organization (WHO) Classification of Thoracic Tumors (1), and it is seen in many slow-growing tumors. However, extensive fibrosis to the degree seen in our cases is not described by the WHO book, and is not well-described in the existing literature (1). It is important to raise awareness of this diagnostic pitfall in mediastinal biopsies (8,9). We present the following cases in accordance with the CARE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-22-15/rc).

Case presentation

Case 1

A 14-year-old male patient presented for workup of shoulder pain and concern for shoulder asymmetry following a sports injury. He denied chest pain and shortness of breath. He had a history of growth hormone deficiency, and was on daily growth hormone replacement therapy. Physical exam was unremarkable, including lack of significant shoulder asymmetry. Single view anteroposterior (AP) chest radiograph incidentally showed a left sided mediastinal contour abnormality concerning for a mediastinal mass. Chest CT with contrast showed a large lobulated, heterogeneous, and vascular left prevascular mediastinal mass isodense to surrounding soft tissue, with internal areas of enhancement (*Figure 1*). Serum AFP and β-hCG were within normal limits. Scrotal Doppler ultrasound study showed no testicular mass. Abdominopelvic magnetic resonance imaging (MRI) and brain MRI were normal.

CT-guided biopsy yielded scant fragments of fibroconnective tissue with variable collagenization and myxoid change (*Figure 2*) associated with irregular and thin ectatic vessels. The stroma was variably cellular and contained reactive myofibroblasts, which were positive on immunohistochemical stains (IHC) for smooth muscle actin (SMA), had mild non-specific reactivity with pancytokeratin AE1/AE3, and were negative for S100 protein. Given the nonspecific findings, additional tissue sampling was performed.

An open biopsy (Chamberlain procedure) showed extensive fibrosclerosis, lymphoplasmacytic inflammatory infiltration, and thin dilated vessels (*Figure 3*). IHC for spalt like transcription factor 4 (SALL4), a pan-germ cell marker, was negative. Cluster of differentiation 34 (CD34), SMA, and desmin highlighted an abundant vascular component. ALK (D5F3), β-catenin, calponin, caldesmon, epithelial

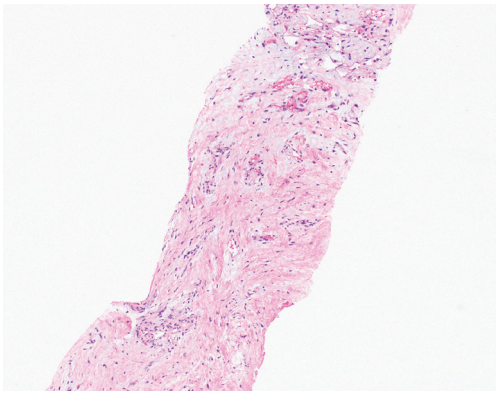

Figure 2 Case 1 first biopsy. CT-guided biopsy was nonspecific. There was scant fibroconnective tissue with variable collagenization, myxoid change, and myofibroblasts (H&E stain; original magnification: 100×). Additional tissue sampling was recommended. CT, computed tomography; H&E, hematoxylin and eosin.

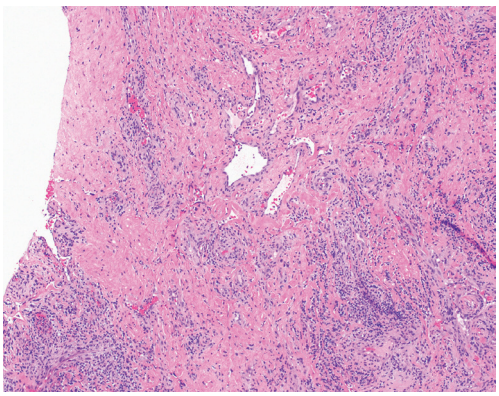

Figure 3 Case 1 second biopsy. Open biopsy showed extensive fibrosclerosis, lymphoplasmacytic infiltration, and thin dilated vessels (H&E stain; original magnification: 100×). H&E, hematoxylin and eosin.

membrane antigen (EMA), and S100 protein were negative. Chromogenic in-situ hybridization for EBV [Epstein Barr virus encoded RNA (EBER)] was also negative. The diagnosis was "vascular fibroblastic/myofibroblastic proliferation consistent with a reactive process".

Complete surgical resection of this lesion by left posterolateral thoracotomy was performed. Gross exam showed a 7.0 cm × 6.9 cm × 4.3 cm irregular circumscribed red-pink firm mass with mottled fibrotic cut surfaces (*Figure 4A*). Microscopic evaluation revealed that the vast majority of the mass consisted of mildly inflamed vascular sclerotic tissue morphologically similar to the previous two biopsies. Only approximately 5% of the total mass contained sheets of medium-sized malignant cells with relatively uniform, large central nuclei with prominent nucleoli, and amphiphilic to clear cytoplasm. The malignant cells were located mostly along the periphery of the mass and involved adjacent thymic parenchyma (*Figure 4B,4C*). IHC showed the tumor cells were diffusely and strongly positive for octamer-binding transcription factor-4 (OCT-4), cluster of differentiation 117 (CD117), placental-like alkaline phosphatase (PLAP) (*Figure 4D-4F*), and podoplanin (D2-40), while negative for AFP and S100 protein. The morphologic and IHC findings were diagnostic of seminoma. Resection margins were negative. One month post-resection, the patient started 4 cycles of chemotherapy (bleomycin, etoposide and cisplatin), which were completed in 80 days. There was no evidence of disease in 3.4 years of post-operative follow-up with serum and imaging studies. *Table 1* summarizes the timeline of events for this patient.

Case 2

A 66-year-old male with history of atrial flutter, Factor V Leiden, and coronavirus disease of 19 (COVID-19) infection (7 months prior) sought emergency care after an episode of syncope. Physical exam was unremarkable. CT pulmonary angiogram demonstrated pulmonary embolism, as well as an incidental large prevascular mediastinal mass with small peripheral calcifications (*Figure 5*). The mass was fluorodeoxyglucose (FDG)-avid on positron emission tomography (PET)-CT, with standardized uptake value (SUV) of 6.3, which was suspicious for malignancy. Upon retrospective review, approximately 50% of the mass was FDG-avid, while the remainder was not FDG-avid. The PET scan showed no evidence of metastatic disease, and no other mass, including in the head, retroperitoneum, coccyx, or scrotum. Seven and a half weeks before biopsy and 9 weeks before surgery, serum LDH was mildly elevated to 317 U/L (reference range, 125–220 U/L); 3.5 weeks before biopsy and 5 weeks before surgery, repeat serum LDH was within normal range. Serum β-hCG, AFP, and CEA levels were within normal limits.

CT-guided biopsy was performed, with the needle (*Figure 6A*) passing through a portion of the mass that was not FDG-avid (*Figure 6B*). The biopsy demonstrated hypocellular dense fibrous tissue (*Figure 6C*). Congo red stain for amyloid was negative. IHC for signal transducer

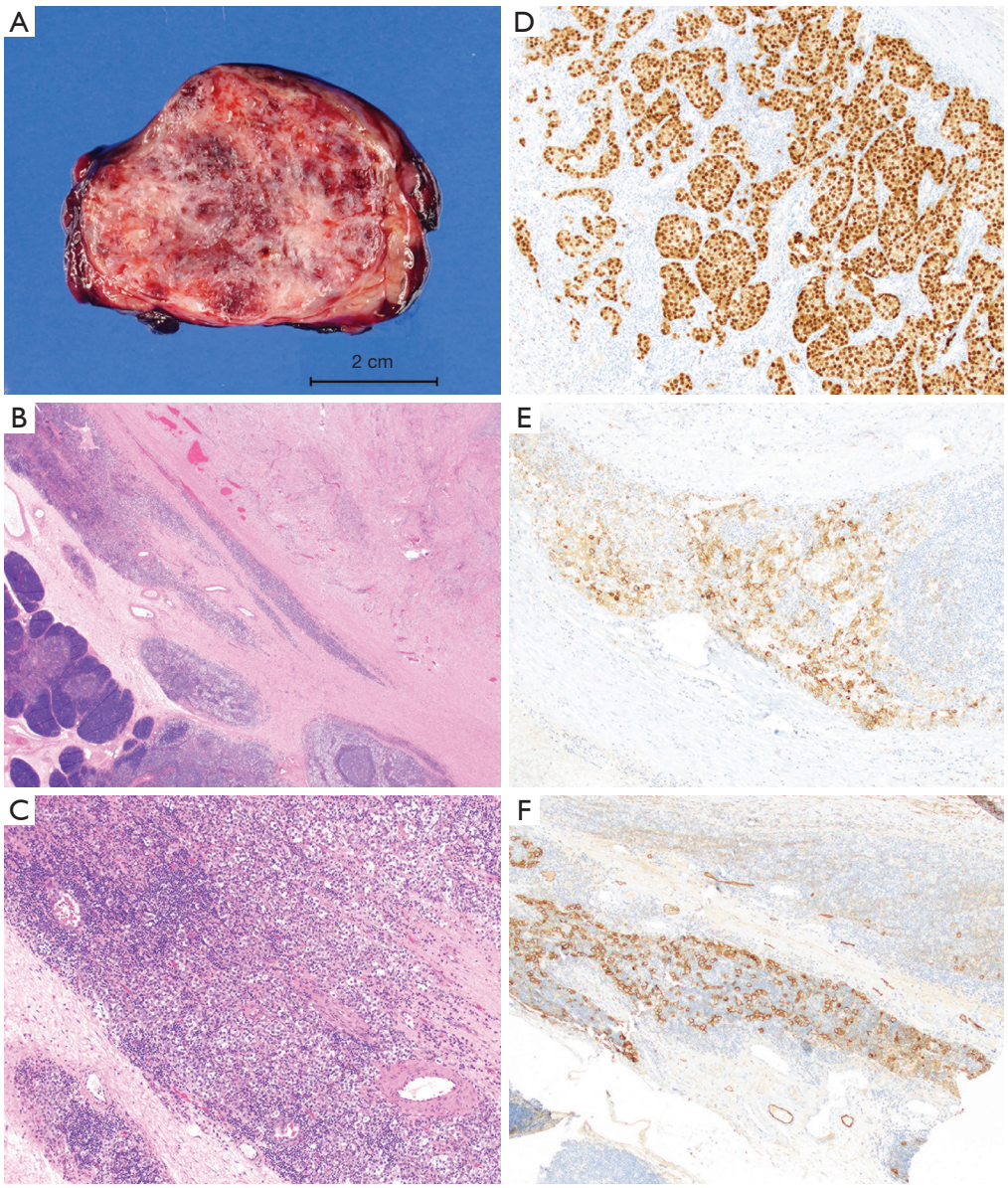

Figure 4 Case 1 resection. Gross examination of the resection specimen showed a 115.6 g, 7.0 cm × 6.9 cm × 4.3 cm irregular well-circumscribed, red-pink firm mass with mottled fibrotic cut surfaces (A). Only approximately 5% of the mass showed tumor cells, mostly along the periphery and involving adjacent thymic parenchyma (B, middle and bottom; H&E stain; original magnification: 20×). The remainder of the mass consisted of inflamed vascular sclerotic tissue suggestive of regression (B, upper right). The tumor component consisted of sheets of medium-sized tumor cells with relatively uniform, large central nuclei with prominent nucleoli, and amphiphilic to clear cytoplasm (C; H&E stain; original magnification: 100×). The tumor cells were positive for immunostains OCT-4, PLAP, and D2-40, consistent with seminoma (D, E, F, respectively; immunohistochemical stains; original magnification: 100×). H&E, hematoxylin and eosin; OCT-4, octamer-binding transcription factor-4; PLAP, placental-like alkaline phosphatase; D2-40, podoplanin.

Table 1 Timeline of events for case 1

Day	Event
−181 (6 months before mass was discovered)	Brain MRI was normal
0	A 14-year-old boy with history of growth hormone deficiency, on daily growth hormone replacement therapy, presented for workup of shoulder pain and concern for shoulder asymmetry after a sports injury. No shoulder abnormality was diagnosed
0	Chest radiograph incidentally discovered a large chest mass
3	Chest CT with contrast showed a large lobulated, heterogeneous, vascular left prevascular mediastinal mass. No lymphadenopathy
6	Serum AFP and β-hCG were normal
8	CT-guided biopsy of the mediastinal mass showed scant fibroconnective tissue with myxoid change, variable cellularity, and irregular thin ectatic vessels. Additional sampling was recommended
13	Open biopsy (Chamberlain procedure) showed extensive fibrosclerosis, lymphoplasmacytic inflammation, and dilated vessels, consistent with a reactive process
29	Complete surgical resection showed a 7-cm seminoma with approximately 95% fibrosis that contained lymphoplasmacytic infiltrates and irregular thin ectatic vessels. The 5% of the mass that contained viable tumor cells was located along the periphery of the tumor, involving adjacent thymic parenchyma. Resection margins were negative
37	US of scrotum was negative
40	MRI of abdomen/pelvis was negative
60 to 140	4 cycles of chemotherapy were completed (bleomycin, etoposide, cisplatin)
1,261 (3.4 years after resection)	No evidence of disease

MRI, magnetic resonance imaging; CT, computed tomography; AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; US, ultrasound.

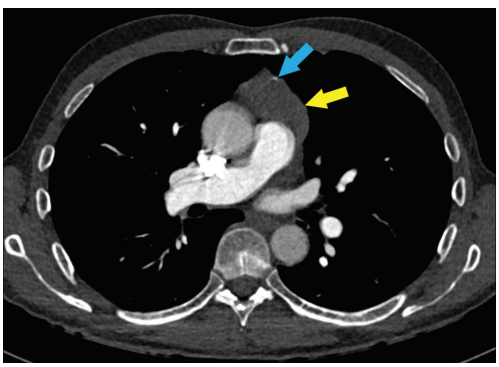

Figure 5 Case 2 imaging. Axial CT angiogram of the chest showed a prevascular mediastinal mass (yellow arrow) with small peripheral calcifications (blue arrow). CT, computed tomography.

and activator of transcription 6 (STAT6), S100 protein, and β-catenin were negative. Flow cytometry analysis was negative for non-Hodgkin lymphoma.

The patient underwent a robotic thymectomy. Gross examination demonstrated a 7 cm × 6 cm × 1.5 cm lobulated tan-white firm tumor with focal hemorrhage (*Figure 7A*). Microscopic exam showed approximately 50% of the tumor consisted of a well-defined region of hypocellular dense fibrous tissue that was similar to what was seen in the preoperative biopsy. The resection additionally showed areas within the fibrosis that contained irregular thin ectatic vessels similar to the first case (*Figure 7B*). The tumor consisted of sheets and nests of medium sized cells separated by fibrous septa. Similar to the first case, the tumor cells also had amphiphilic to clear cytoplasm with relatively uniform, large central nuclei and prominent nucleoli. A lymphoplasmacytic infiltrate was seen in the fibrous septa (*Figure 7C*). IHCs showed the tumor cells were positive for OCT-4 (*Figure 7D*), CD117 (*Figure 7E*), SALL4 (*Figure 7F*), pancytokeratin CAM 5.2 (dot-like cytoplasmic pattern), and D2-40, while negative for Glypican-3 and cluster of differentiation 30 (CD30), which confirmed the diagnosis of seminoma. The resection margin was focally positive. No lymph node metastasis was present. Three and a half

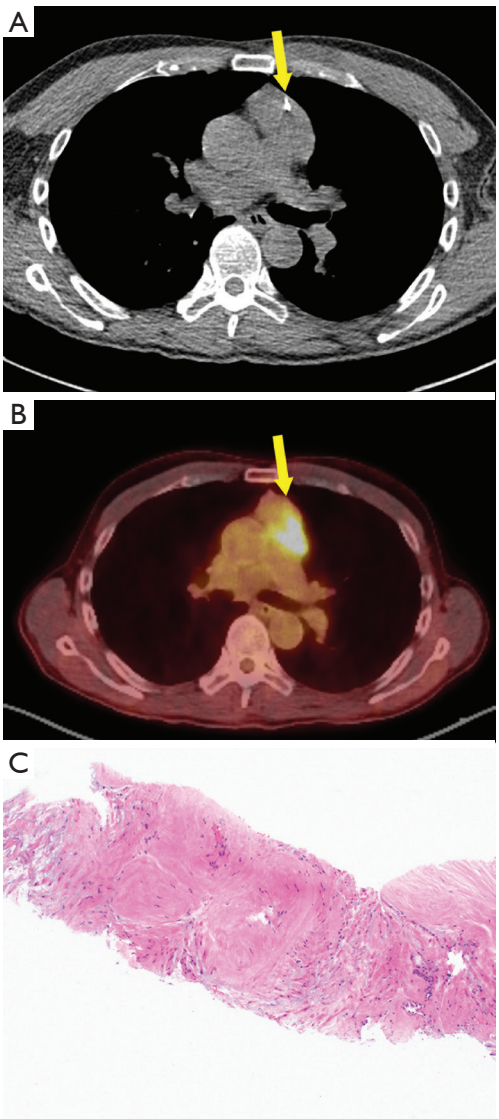

Figure 6 Case 2 biopsy. During CT-guided biopsy, the needle (A, arrow) entered a non-FDG-avid portion of the mass (B; PET scan; arrow corresponds to biopsied area shown in A). The biopsy demonstrated hypocellular dense fibrous tissue (C; H&E stain; original magnification: 100×) that was negative for Congo red, STAT6, S100 protein, and β-catenin. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; H&E, hematoxylin and eosin.

months post-resection, the patient underwent 4 cycles of chemotherapy (etoposide and cisplatin), which were completed in 67 days. There was no evidence of disease in 1 year of post-operative follow up with serum and imaging studies. *Table 2* summarizes the timeline of events for this patient.

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). The study was approved by the institutional review board of New York University (No. S21-01220), and individual consent for this retrospective analysis was waived.

Discussion

Summary & literature review

We have provided what is to date the most detailed clinicopathologic description of two cases of primary mediastinal seminoma with tumor regression. The regressed areas were sampled on biopsy and hindered accurate preoperative diagnosis. Spontaneous tumor regression is a rare phenomenon, and its real incidence is difficult to estimate (10). There is no standard for grading regression. Some have proposed scoring tumor regression according to the volume of radiation-induced or idiopathic (in our cases) fibrosis (7). The underlying mechanisms are unknown. One theory is that it is mediated by immune system activation (11), and some hypothesize it may be akin to a wound-healing process (12). It is well-described in gonadal seminomas, and is recognized in the WHO Classification of Tumors of the Urinary System and Male Genital Organs (13). For mediastinal germ cell tumors, although fibrous septa/stroma is mentioned in the WHO Classification of Thoracic Tumors (1), this type of limited fibrosis is seen in many slow-growing tumors. Extensive fibrosis to the degree consistent with tumor regression, as seen in our cases, is not described by the WHO, and is not well-described in the existing literature (1). It is important to raise awareness of this diagnostic pitfall in mediastinal biopsies (8,9).

In the testis, germ cell tumor regression usually manifests histologically as a well-defined to irregular nodular focus/foci of scar or fibrosis with various combinations of fibrosis, neovasculature, mixed chronic inflammation, calcification, and/or giant cell reaction (13-16). Both of our cases of mediastinal seminoma demonstrated histologic findings that correspond to the features of regression described in gonadal germ cell tumors. They both contained extensive areas of well-defined fibrosis with inflammation and irregular thin-walled ectatic vessels (consistent with neovasculature). In addition, there was transient elevation of serum LDH in patient #2, followed by spontaneous

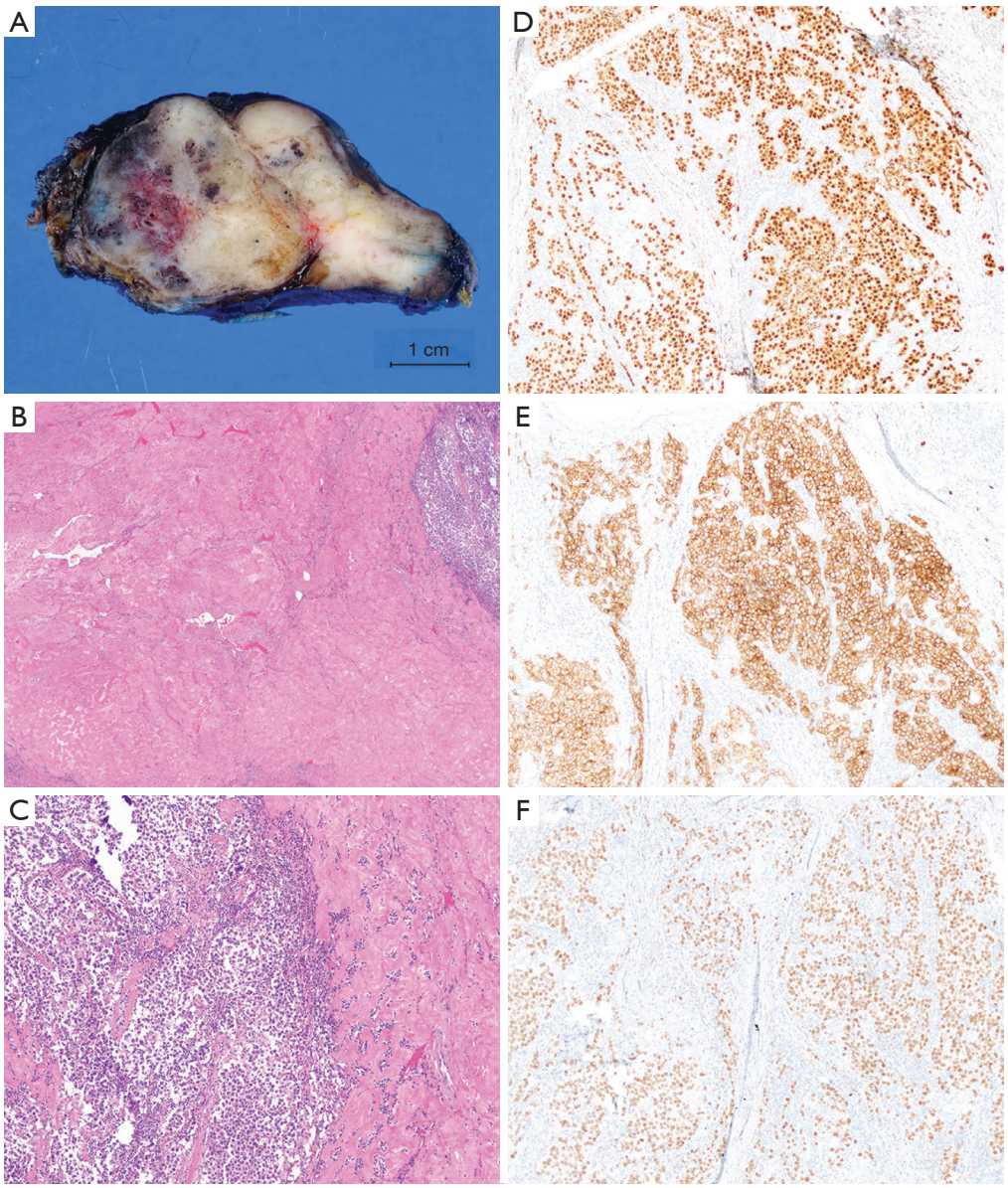

Figure 7 Case 2 resection. Gross examination of the resection specimen showed a 7.0 cm × 6.0 cm × 1.5 cm tan-white lobulated firm tumor with focal hemorrhage on cut sections (A). Approximately 50% of the tumor showed dense hypocellular fibrotic tissue with irregular thin ectatic vessels, suggestive of regression (B, left; H&E stain; original magnification: 40×). The tumor consisted of sheets and nests of medium sized tumor cells separated by fibrous septa. The tumor cells had amphiphilic to clear cytoplasm with relatively uniform, large central nuclei and prominent nucleoli. A lymphoplasmacytic infiltrate was seen in the fibrous septa (C; H&E stain; original magnification: 100×). The tumor cells were positive for immunostains OCT-4, CD117, SALL4 (D, E, F, respectively; immunohistochemical stains; original magnification: 100×), keratin CAM 5.2 (dot-like cytoplasmic pattern), and D2-40, while negative for Glypican-3 and CD30, consistent with seminoma. H&E, hematoxylin and eosin; OCT-4, octamer-binding transcription factor-4; CD117, cluster of differentiation 117; SALL4, spalt like transcription factor 4; D2-40, podoplanin; CD30, cluster of differentiation 30.

Table 2 Timeline of events for case 2

Day	Event
0	A 66-year-old man with history of atrial flutter, Factor V Leiden, and COVID-19 infection (seven months prior) sought emergency care after an episode of syncope
0	CT angiogram showed pulmonary emboli, and incidentally discovered a prevascular mediastinal mass
1	Serum β-hCG, AFP, and CEA levels were normal
22	Serum LDH was elevated to 317 U/L (reference range, 125–220 U/L)
49	Serum LDH decreased to normal
50	PET/CT scan showed the mass had an SUV of 6.3 which was suspicious for malignancy. There was no evidence of metastatic disease or mass elsewhere, including the head, retroperitoneum, coccyx, or scrotum
	In hindsight, approximately 50% of the mediastinal mass showed lack of FDG avidity, corresponding to 50% of the tumor being fibrotic on pathologic examination of the resection specimen
73	CT-guided biopsy showed hypocellular dense fibrous tissue.
85	Surgical resection showed a 7-cm seminoma with approximately 50% fibrosis corresponding to the non-FDG avid portion of tumor on PET scan. Lymphoplasmacytic infiltrates and irregular thin ectatic vessels were present in the fibrosis. Focally positive resection margin. Benign lymph nodes
189 to 256	4 cycles of chemotherapy were completed (etoposide, cisplatin)
455 (1 year after resection)	No evidence of disease

COVID-19, coronavirus disease of 19; CT, computed tomography; hCG, human chorionic gonadotropin; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; PET, positron emission tomography; SUV, standard uptake value; FDG, fluorodeoxyglucose.

normalization; and upon retrospective review of the PET-CT scan and biopsy needle placement, the fibrotic region corresponded to a non FDG-avid region of the tumor. It is based on these facts that we propose the extensive fibrosis seen in our cases is consistent with regression (7).

In the existing English language literature, only two cases of mediastinal germ cell tumor with spontaneous regression have been reported (*Table 3*). In both cases, serum β-hCG was initially elevated, followed by normalization before any therapy was initiated. CT scans in both cases showed concomitant tumor size decrease as the serum hCG levels decreased. Histologic exam of one resected case showed combined teratoma and seminoma with evidence of regression in the form of fibrous granulation tissue (8). The other case was diagnosed on open biopsy, followed by chemotherapy and resection; histologic features of regression were not described in the paper (9).

Clinical relevance and differential diagnosis

Clinically, the differential diagnosis of an anterior/prevascular mediastinal mass includes (I) benign entities such as enlarged or ectopic thyroid tissue, thymic hyperplasia, and ectopic parathyroid tissue; (II) primary neoplastic diseases including thymic epithelial neoplasms, thymic neuroendocrine neoplasms, lymphoma, and extragonadal germ cell tumor; (III) metastatic disease; as well as (IV) inflammatory diseases, such as infection, lipid storage disease, sarcoidosis, fibrosing mediastinitis, immunoglobulin G subclass 4-related disease (IgG4-RD), histiocytosis X, and Castleman disease (17,18). Biopsy of the lesion is preferred for diagnosis, and contributes to the decision of whether to pursue surgical resection, radiation, or systemic therapy. The sensitivity and specificity of biopsies, including fine needle aspiration, for the diagnosis of mediastinal lesions is very good, although cystic and inflammatory conditions have lower sensitivity (19).

The presence of fibrous tissue in a mediastinal biopsy raises the possibility of the following entities in the pathologic differential diagnosis: fibrosing mediastinitis; IgG4-RD; Hodgkin lymphoma; as well as reactive fibrotic and inflammatory changes within or adjacent to other processes.

Fibrosing mediastinitis, or "sclerosing mediastinitis", is a rare cause of mediastinal masses (20), and is regarded as an abnormal wound-healing response to triggers including

Table 3 Literature review of spontaneous regression in mediastinal germ cell tumors

Paper	Demographics and presentation	Preoperative serum tumor markers	Radiology	Pathology	Chemotherapy	Follow-up after surgery
Hachiya *et al.* 1998, (8)	A 22-year-old man Routine chest radiograph 4-month history of anterior chest pain	Serum hCG was 20 mIU/mL (reference range <1.0 mIU/mL), followed by normalization after needle aspiration biopsy	Postcontrast CT showed the mass decreased in size (unspecified) after needle aspiration biopsy, as serum hCG normalized. A large, low-density area developed	Needle aspiration biopsy was nondiagnostic. Surgical resection showed combined teratoma and seminoma, invading right upper and middle lung lobes, part of pericardium, bilateral brachiocephalic veins, and superior vena cava. No metastasis. Complete resection was achieved. "Most" of the tumor showed regression (fibrous granulation tissue) and large foci of necrosis. Thymic tissue was seen in the mass	Post-surgery: cisplatin, peplomycin, vinblastine	Alive without evidence of recurrence in more than 10 years
Yu *et al.* 2017, (9)	A 37-year-old man Routine chest radiograph Anterior chest discomfort when bending forward	β-hCG 5.9 mIU/mL (reference range <1.0 mIU/mL), followed by spontaneous normalization to 0.9 mIU/mL	CT showed size initially increased from 75 to 83 mm, then decreased to 65 mm as the β-hCG normalized	VATS biopsy showed seminoma. Histopathologic features of regression were not described in the paper. Tumor was fully resected after chemotherapy	Pre-surgery: bleomycin, etoposide, cisplatin	Alive without evidence of recurrence in 2 years
Current paper	A 14-year-old boy Chest radiograph in workup of shoulder pain following a sport injury	β-hCG and AFP within normal limits	CT with contrast showed a heterogeneous mass with internal areas of enhancement	CT-guided and open biopsies were nondiagnostic, showing inflamed sclerotic tissue with irregular thin ectatic vessels. Surgical resection showed seminoma involving thymus. 95% of the tumor showed inflamed vascular sclerotic tissue suggestive of regression. Margins negative	Post-surgery: bleomycin, etoposide, cisplatin (4 cycles)	Alive without evidence of recurrence in 3.4 years
Current paper	A 66-year-old man Chest CT-angiogram in workup of syncope	LDH was elevated to 317 U/L (reference range, 125–220 U/L), followed by spontaneous normalization. β-hCG, AFP, CEA within normal limits	CT pulmonary angiogram showed a mass with small peripheral calcifications. PET scan showed approximately 50% was FDG-avid (SUV 6.3) while the remainder of the tumor was not FDG-avid	CT-guided biopsy of non-FDG-avid region was nondiagnostic, showing dense fibrotic tissue. Surgical resection showed seminoma with 50% hypocellular dense fibrosis with irregular thin ectatic vessels suggestive of regression. Focal positive margin. No nodal metastasis	Post-surgery: cisplatin and etoposide (4 cycles)	Alive without evidence of recurrence in 1 year

hCG, human chorionic gonadotropin; CT, computed tomography; VATS, video-assisted thoracoscopic surgery; AFP, alpha fetoprotein; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; PET, positron emission tomography; FDG, fluorodeoxyglucose; SUV, standard uptake value.

histoplasmosis (in which case granulomas may be found), other fungal infections, tuberculosis, autoimmune diseases, and radiation. Radiographically, it often presents as an infiltrative process (21). In most cases, a cause cannot be found; in such idiopathic cases, some presume there may be an undiagnosed underlying infection, autoimmune disease, or IgG4-RD. Histologically, fibrosing mediastinitis can show a range of fibrotic and mixed chronic inflammatory changes that resemble the stages of wound healing (22,23). The fibrosis can consist of fibromyxoid tissue with numerous spindle cells and thin-walled vessels (similar to case 1); or it can consist of thick glassy bands of haphazardly arranged collagen with only focal spindle cells; or it can contain dense hypocellular collagen and occasional dystrophic calcification (similar to case 2). Some have postulated that tumor regression may also be a sort of wound-healing process (12). Unless tumor cells are sampled in the biopsy, it is not possible to separate fibrosing mediastinitis from tumor regression histologically.

IgG4-RD is an autoimmune systemic fibroinflammatory disease characterized by storiform fibrosis with lymphoplasmacytic infiltration, phlebitis, and increased numbers of IgG4-positive plasma cells. Elevated serum levels of IgG4 may or may not be present (24,25). IgG4-RD has been described in the mediastinum (26,27). In our cases, there were no elevated numbers of plasma cells in the biopsies to suggest this diagnosis.

Nodular sclerosis (classical) Hodgkin lymphoma is the most common type of lymphoma to affect the mediastinum. Histologically, the tumor is characterized by nodules of polymorphous inflammatory cells surrounded by broad fibrous bands. Reed-Sternberg cells are required for histopathological diagnosis. Similar to seminoma, poorly-formed granulomata can be seen in association with classical Hodgkin lymphoma. The presence of extensive sclerosis in biopsy specimens can also hinder the diagnosis of this entity.

Conclusions

In cases like ours where fibrosis comprises the majority of the lesion, biopsy diagnosis can be very challenging. The biopsy sample may not reveal the true nature of the lesion that may be present nearby, even with the use of ancillary studies such as immunohistochemistry. Pathologists should always question whether the observed findings account for the entire lesion, or represent reactive or fibrotic changes associated with a different underlying lesion. Here we also postulate that primary mediastinal seminomas can contain extensive areas of fibrosis (beyond just fibrous septa/stroma) consistent with tumor regression. Prospective knowledge of this diagnostic pitfall and attempts to target biopsies toward FDG-avid portions of a mediastinal mass may increase diagnostic yield and accuracy, thereby helping to prevent non-indicated surgical interventions.

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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). The study was approved by the institutional review board of New York University (No. S21-01220), and individual consent for this retrospective analysis was waived.

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Editorial Commentary

The European Reference Network: the keystone for the management of rare thoracic cancers

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Rare tumors are a heterogeneous group of malignancies, which show an incidence rate of <6 per 100,000 people per year, according to the definition of Surveillance of Rare Cancers in Europe (RARECARE) (1).

Overall, the estimated incidence of all rare tumors in Europe accounts for 24% of all cancers, with 5-year relative survival for all rare cancers of 48.5% (2).

Indeed, rare thoracic tumors include many entities: epithelial tumors of the trachea, rare epithelial tumors of the lung, epithelial tumors of the thymus, malignant pleural and pericardial mesothelioma, mediastinal germ cell tumors and mesenchymal tumors (*Table 1*) (1,3-5).

The incidence of these tumors in Europe is the highest in patients aged 65 years and older, with a crude rate of 1.4 per million per year for the epithelial tumor of the trachea, 1.7 per million per year for thymic epithelial tumors, among which malignant thymomas are the most common, and 16 per million per year for the malignant mesothelioma of pleura and pericardium. The 5-years relative survival rate is 14% for the epithelial tumors of the trachea, 65.6% for thymic epithelial tumors, and 5.4% for malignant mesothelioma (5). Detailed data on incidence, prevalence and survival of several types of rare thoracic tumors included in *Table 1* were reported in a study of the RARECARE working group, using a large patient database (5).

These malignancies present an intrinsic complexity in clinical management, both in the initial diagnostic phase, as well as in the treatment choice, due to scarcity of clinical practice guidelines and also to the lack of randomized clinical trials, which substantially limit treatment options. Moreover, to reduce the diagnostic delay and to improve the appropriateness of treatment choice, clinical centers with adequate patient volumes and expertise should be homogeneously accessible in different geographical areas, also to reduce healthcare migration (3,6,7).

Notably, the clinical complexity of rare thoracic tumors systematically requires multidisciplinary team discussion to reach the correct diagnosis and offer the best treatment.

In 2008, the European Commission launched the RARECARE project. This is a population-based cancer registry aiming at defining incidence, prevalence and long-term outcome of rare cancers. This project allows to study the epidemiology of these cancers in a large and heterogeneous population (8,9). The results of RARECARE registry led to a second project (RARECAREnet), which updated and enlarged the available information on rare cancers in Europe (10).

In addition, the Joint Action on Rare Cancers (JARC) launched in 2016, is another major European initiative, in which 34 partners from different countries belonging to the European Community are involved. This project, coordinated by the National Cancer Institute of Milan (INT), seeks to improve the epidemiological knowledge of rare cancers, to offer education to healthcare professionals and to ameliorate clinical management of these diseases, promoting the integration of translational research

Table 1 Rare tumors of the thoracic cavity (1,3-5)

Tier	Name
1	Epithelial tumours of trachea
2	Squamous cell carcinoma and variants of trachea
2	Adenocarcinoma and variants of trachea
2	Salivary gland type tumours of trachea
1	Epithelial tumour of thymus
2	Malignant thymoma
2	Squamous cell carcinoma of thymus
2	Undifferentiated carcinoma of thymus
2	Lymphoepithelial carcinoma of thymus
2	Adenocarcinoma and variants of thymus
2	Neuroendocrine tumors
2	Thymic carcinoma
2	Salivary gland like carcinoma
2	NUT carcinoma
1	Malignant mesothelioma
2	Mesothelioma of pleura and pericardium
1	Epithelial tumours of lung
2	Adenosquamous carcinoma of lung
2	Large cell carcinoma of lung
2	Well differentiated endocrine carcinoma of the lung
2	Poorly differentiated endocrine carcinoma of the lung
2	Squamous cell carcinoma with variants of lungs
2	Bronchiolo-alveolar carcinoma of lung
2	Undifferentiated carcinoma of lung
2	Salivary gland type tumours of lung
2	Sarcomatoid carcinoma of lung
1	Mediastinal Germ cell tumors
1	Mesenchymal tumors
2	Adipocytic tumors
2	Fibroblastic and myofibroblastic tumors
2	Vascular tumors
2	Skeletal muscle tumors
2	Peripheral nerve sheath and neural tumors
2	Tumors of uncertain differentiation

NUT, nuclear protein of the testis.

innovations into rare cancer care and ensuring sharing of best practices and equality of care across European countries (10).

An important milestone was set in 2017, when the European Reference Networks (ERNs) were established as a pan-European initiative to ensure and improve the most appropriate care for patients with rare or low prevalence diseases. It is expected that bringing together European reference centers within an official network, patients with rare diseases could get more often and more quickly access to expert care and that guideline development and research discoveries could be facilitated (11).

Twenty-four ERNs have been approved, involving more than 900 highly-specialized healthcare providers from over 300 hospitals in 26 EU countries (11,12).

There are four ERNs with an oncological focus: the ERN EuroBloodNet on rare hematological diseases, the ERN Genturis on genetic tumor risk syndromes, the ERN PaedCan on pediatric cancer (haemato-oncology), and the ERNs for Rare Adult Solid Cancer (ERN-EURACAN) (12).

At present, the ERN-EURACAN has 75 full members and affiliated partners from 24 countries, 30 associated partners and covers 10 disease domains, corresponding to the list of rare adult solid cancer (RARECARE) based on the international classification of disease (ICD-10) (12,13).

In agreement with the basic principles of the ERN, the objectives of EURACAN are to reduce disparities and guarantee equal access to the treatment for rare tumors among different member states of the European Community to increase the quality of care of rare cancer patients. All these purposes might be obtained through infrastructures with a high level of multidisciplinary expertise (5,13,14). The European network collects and edits available information through the creation of large cancer registry population data, which has contributed in recent years to a significant improvement in the knowledge of these tumors and produces new scientific evidence by conducting clinical and translational research.

Within the ERN-EURACAN, according to the last accessible assessment report, the rare thoracic tumor domain (G8 domain) is structured in 20 centers (*Table 2*) with expertise in the management of these rare tumors (15). The difficulties encountered in the management of rare thoracic cancers are in part in common with those encountered for other rare diseases and include the aforementioned lack of data about the biology of these groups of tumors, late

Table 2 List of expert centers for rare thoracic cancer (14)

Country	Institution
Belgium	Antwerp University Hospital, Edegem
Italy	Azienda Ospedaliera Universitaria Senese, Siena
Italy	Azienda Ospedaliero–Universitaria Città della Salute e della Scienza di Torino, Turin
Luxembourg	Centre Hospitalier de Luxembourg, Luxembourg
Italy	Centro di Riferimento Oncologico di Aviano, Aviano
Italy	Rare Tumors Coordinating Center of Campania Region (CRCTR), Naples
Italy	Fondazione IRCCS Istituto Nazionale dei Tumori, Milan
France	Hospices Civils de Lyon, Lyon
France	Institut Gustave Roussy, Villejuif
Belgium	Institut Jules Bordet, Brussels
Italy	IRCCS San Martino–IST, Genoa
Italy	Istituto Fisioterapici Ospitalieri, Rome
Italy	Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola
Belgium	Leuven Cancer Institut, Leuven
Germany	Mannheim University Medical Center, Mannheim
Malta	Mater Dei Hospital, L-Imsida
The Netherlands	Netherlands Cancer Institute–Antoni van Leeuwenhoek, Amsterdam
Estonia	North Estonia Medical Centre foundation, Tallin
Estonia	Tartu University Hospital, Tartu
Germany	University Hospital Essen, Essen

diagnosis, pathological misdiagnosis, incorrect management, and absence of effective and standardized evidence-based treatment.

Since its establishment, the G8 domain has worked to overcome these pitfalls, through a vast range of activities, such as involving new reference centers, launching large projects for the creation of shared clinical databases in collaboration with other international groups (i.e., the International Thymic Malignancy Interest Group; ITMIG), promoting novel translational and clinical research programs through international collaborations, creating web-based-platforms for multidisciplinary case discussion, promoting different educational program for medical, radiation and surgical oncologists (16,17).

The discovery of aberrations in the oncogenic driver genome has changed the therapeutic algorithm of many tumors that need to be characterized by precision oncological methodology and could represent a keystone in the treatment of rare thoracic tumors that present little therapeutic possibilities. In this scenario, the EURACAN G8 domain recently launched a project named the real-world European registry to collect data from adult cancer patients harboring NTRK gene fusions and other rare actionable gene aberrations (TRacKING) together with a European registry to describe the management of patient with solid cancers harboring a NTRK fusion or other rare actionable fusion (17). In the same way other projects such as the lungNENomics and panNENomics on neuroendocrine tumors, and MESomics on mesothelioma, are carried out in partnership with the International Agency for Research on Cancer (IARC) with the establishment of the Rare Cancer Genomics group and focus on the molecular characterization of rare thoracic cancers. These projects will offer further information useful for dissecting the molecular biology of these tumors thus leading to potential improvement in targeted drug development (17-19).

More recently, despite the difficulties related to the restrictions due to COVID-19 pandemic, officially declared on March 11th 2020 by the WHO, which affected negatively not only clinical and translational research activities, but also the diagnosis and treatment of oncological patients (20), the members of the ERN-EURACAN continued to support and help in the research and management of patients suffering from rare thoracic tumors.

Indeed, thoracic tumors, for their natural history and the treatment procedures, could cause serious respiratory and cardiovascular complications such as invasion of the lung and pleura, atelectasia due to compressive effect, reduced respiratory function due to surgical procedures that could be further aggravated by concomitant COVID-19 infection. A tailored risk assessment strategy for thoracic cancer patients, including those with rare tumors, has been recommended and several studies have been conducted, including the published study TERAVOLT, a longitudinal multi-center study on thoracic cancer patients who experienced COVID-19 (21).

Therefore, the networking of national Centers of competence at European level and the collaboration with various international groups represent the best option possibility to support rare tumor patients, as these diseases are heterogeneous in biological and clinical features, to have access to a correct, timely diagnosis, as well as to appropriate and most up-to-date care, including the possibility of having access to clinical trials and to the second opinion of specialists, guaranteeing equal access and better management.

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Editorial Commentary

Multidisciplinary approach for rare thoracic tumors during COVID-19 pandemic

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic started in March 2020 (1) and since then it has dramatically changed the diagnostic and therapeutic management of many chronic diseases, including cancer. During the first lockdown, overwhelmed healthcare systems could not guarantee regular access to early cancer diagnosis screening campaigns, as well as to clinical and radiological follow-up of cancer patients, causing a potential diagnostic and therapeutic delay (2), whose effects have been seen in the short-term and may continue to be seen for the next few years. However, life-saving cancer therapies were among the few health services guaranteed, even during the hardest phase of pandemic, as they have been made accessible by implementing effective triage procedures (3).

In this commentary, we describe the peculiar clinical features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with rare thoracic tumors, including thymic epithelial tumors (TET) and mediastinal germ cell tumors, and focus on the importance of multidisciplinary clinical management of these diseases.

Multidisciplinary treatment for patients with thymic epithelial and mediastinal germ cell tumors and concomitant SARS-Cov-2 infection

The SARS-Cov-2 infection can influence diagnostic and therapeutic choices in cancer patients, which are mostly related to the organs involved by primary/metastatic disease and the specific toxicity expected with administration of anti-cancer treatments. For patients with rare thoracic tumors, the management of COVID-19 and its short- and long-term complications can be particularly challenging.

Mediastinal primary tumors are rare cancers, usually diagnosed in patients between 30 and 50 years old, although they can occur at any age and from any tissue present in the mediastinum. Mediastinal tumor mass can be often asymptomatic for long term; thus incidental diagnosis can frequently occur. In the course of the current pandemic, mediastinal masses were often accidentally identified during evaluation of lung involvement by COVID-19 through imaging methods. This may also generate difficulties in differential diagnosis, as modest dimensional increase of the thymic gland may be due to post-infection hyperplasia (4). In these cases, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showing low tracer uptake can be useful in supporting the diagnostic hypothesis of thymic hyperplasia (5). Mass size may also be indicative, as a reduction in mediastinal masses identified by short-term computed tomography (CT) scan may be another differential criterion between thymic hyperplasia and TET (6).

When patients suffering from mediastinal tumors, who have already been diagnosed and are undergoing treatment, contract SARS-Cov-2 infection, the treatment

of COVID-19 becomes a priority over the anti-tumor treatment. This may lead to interruption or delay of cancer therapies. A survey was conducted among oncologists working at international expertise centers, with the aim of optimizing the management of germ cell tumors during the pandemic and identifying different approaches based on experience of each individual country. This study concluded that chemotherapy should be withheld until the acute phase of COVID-19 has resolved or there are no more respiratory symptoms (7). However, most treatments in oncology cannot be safely postponed for long time, particularly when complete recovery is achievable and delay of treatment can jeopardize its efficacy, such as in the case of germ cell tumors, or when the patient is at immediate risk, due to life-threatening disease. This can happen in patients with large mediastinal masses and severe impairment of cardio-respiratory function. In these cases, it may be reasonable to hold the antineoplastic treatment just until the patient overcomes the acute infectious disease phase and then to proceed with the planned treatment, even with a positive molecular swab (8). In support of this approach, a meta-analysis showed that no viable virus could be isolated from culture beyond day 9 of illness, despite the presence of persistently high viral RNA loads (9). In our opinion, decision-making concerning anticancer treatment (i.e., chemotherapy) and procedures (surgery, radiotherapy) must be closely evaluated against the risks linked to cancer progression and should be evaluated case by case, especially if the interrupted anti-cancer treatments are potentially curative. In addition, the American Society of Clinical Oncology (ASCO) guidelines suggest that specific areas and dedicated personnel should be designated for the treatment of COVID-19 patients and treatment restarted at an isolated infusion center, away from the main infusion center (10).

Regarding the type of treatment of germ cell tumors, the classical schedule including bleomycin, etoposide and cisplatin (BEP) remains a valid option since the omission of bleomycin, due to the risk of respiratory failure and pneumonitis, has no clear indication (7). There are not enough data about the use of immune checkpoint inhibitors (ICIs) during pandemic but this treatment does not appear to be an additional risk factor for severe COVID-19 in patients with cancer (11,12). Moreover, a multicenter observational study showed that the administration of anti-cancer treatment, including chemotherapy, ICIs, and tyrosine kinase inhibitors (TKIs) did not affect survival in patients with COVID-19 (13).

According to our experience, another issue of critical importance in patients with mediastinal tumor and SARS-Cov-2 infection is defining the optimal management of respiratory and cardiovascular symptoms. Mediastinal tumors can cause serious respiratory and cardiovascular complications, due to tumor invasion of the lung, pleura, heart, pericardium and large vessels, with an increased risk of thrombosis or bleeding, to atelectasis due to compressive effect, and to reduced respiratory function due to previous surgery. Moreover, during the first phase of the pandemic a meta-analysis showed that cancer patients are at a higher risk of thromboembolic events and associated complications, such as lung vessel obstructive thrombo-inflammatory syndrome (14). Therefore, cancer patients with SARS-Cov-2 symptomatic infection may need a personalized clinical management, overseen by a multidisciplinary clinical team. This includes close monitoring and re-evaluation of oxygen therapy, with or without high flow and continuous positive airway pressure (CPAP) (15). In addition, anticoagulant thromboprophylaxis with low-molecular-weight heparin (LMWH) or fondaparinux may be recommended (16), but it needs to be carefully evaluated in patients at high risk of bleeding. Further, the management of patients with risk factors for severe COVID-19 (including chronic lung disease, heart failure and active anticancer therapy) changed since the approval of monoclonal antibodies anti SARS-Cov-2 for the treatment of mild cases (17). However, to date, there are no published reports focusing on the use of monoclonal antibodies in patients with rare cancers.

Finally, as vaccine availability has dramatically changed the epidemiology of SARS CoV-2 infection in general population, vaccination is strongly recommended also in cancer patients, according to the European Society of Medical Oncology (ESMO) statements, since it has been shown to be safe and effective in this frail population. For the same reasons, vaccine booster dose should always be considered in cancer patients (18).

Concluding remarks and future prospective

In the current pandemic scenario, cancer-related information like staging, grading, setting of therapy, comorbidities, type of cancer therapy, type of treatment for SARS-Cov-2 infection should be evaluated by a multidisciplinary working team as a key strategy for the management of rare thoracic tumors.

Future research should focus on collecting all the basic characteristics of rare cancer patients with COVID-19,

tumor biology, chemotherapy/radiation-related variables, and the biochemical and inflammatory profile of these patients during infection.

Finally, the limitations in patient hospitalization and access to high expertise centers imposed by COVID-19 pandemic demand the implementation of novel approaches of care, such as telehealth and digital health in oncology. Cross-border teleconsultations by individual healthcare providers within expert tumor networks could be an excellent tool to improve medical education and ultimately clinical outcome of patients with rare tumors during COVID-19 era (19).

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Extended Abstract

Advances in thoracic surgery for thymic tumors: extended abstract

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Most thymic tumors are thymomas and they are found either incidentally or with diagnostic workup for myasthenia gravis (MG). There are 4 typical radiological findings: (I) the small mediastinal tumor with a more or less central position well surrounded by thymic tissue, (II) the large but well-confined tumor with visible or anticipated tissue layers between the tumor and pericardium, lung, and sternum as well as the larger vessels, (III) the thymic tumor with an irregular shape, without tissue layers as margin to the other mediastinal organs, and supposedly showing tumor, node, metastasis (TNM) stage III features during mediastinal dissection or at least being in close contact with the phrenic nerve, and (IV) a tumor with primary questionable resectability and requiring a biopsy for differential diagnosis before the therapeutic decision.

Open surgery *vs.* minimally invasive surgery (MIS)

A meta-analysis of published reports between 1995 and 2014 analyzed MIS versus open surgery for thymoma and found MIS thymectomy to be safe and to achieve similar oncological results compared to open thymectomy for selected patients with thymic malignancy (1).

The actual report from the European Society of Thoracic Surgeons (ESTS) database compared retrospective data between 1990–2010 with prospective data between 2007–2017. The increased percentage of MIS thymectomies from 6 to 33% contained robotic surgery (2% to 13%) (2).

Increasing numbers of robotic, as well as thoracoscopic non-robotic thymectomies (6% to 14% and 8% to 15%, respectively), were registered in the US between 2010–2014. With propensity-matching analysis, there were no differences in the 5-year overall survival (OS) rate between robotic-assisted thymectomy and thoracoscopic non-robotic thymectomy (3). Another national database analysis confirmed equal 5-year survival of open and MIS thymectomy (4). Most of the actual literature summarized data of patients operated on until nearly 5 years back, therefore, according to the general acceptance of MIS, the namely robotic-assisted technique for thoracic surgery, a further tremendous increase in MIS for thymic epithelial tumor (TET) can be expected by looking at actual records.

A meta-analysis investigating the influence of the surgical technique for thymectomy on complete stable remission (CSR) in MG has shown solid evidence for MIS thymectomy. Extended minimally invasive techniques were found to have CSR rates comparable to extended transsternal techniques in patients with thymoma, and are thus suitable in the hands of skilled surgeons (5).

Tumor size has a potential impact on the prognosis of patients with thymoma

In terms of tumor size, a single-center study of 154 patients found that thymoma size >4 cm was an independent predictive predictor for progression, which was also shown in TNM stage I thymoma (6). No difference in mid-term oncological results with robotic thymectomy for large thymoma (n=39, mean 6.2 cm) compared to small thymoma (n=42, mean 2.9 cm) was found with a cut-off at 4 cm of size (Charité-Universitätsmedizin Berlin, unpublished data).

Repeatedly the feasibility of robotic thymectomy for larger thymoma as compared to sternotomy has been shown (7,8). A technical recommendation for the larger thymomas

is the use of a 4-trocar-robotic approach including the subxiphoid entrance.

The Korean Association for Research of the Thymus accomplished another four-center research on limited thymectomy for early-stage thymoma. Limited thymectomy was not inferior to complete thymectomy in 295/762 patients with early-stage thymoma in terms of recurrence (9). Large thymoma and limited thymectomy appear to be related to an increased risk of MG after surgery. Patients with thymoma should have their acetylcholine receptor antibody (AchR-Ab) levels evaluated before and after surgery (10).

Surgery-related aspects with TETs

The extent of surgical resection and the choice of whether to perform lymph node dissection also have an impact on the clinical prognosis of patients with TETs. Among 13/131 patients with lymph node involvement, only patients with thymic carcinoma (25%) or B2/B3 thymoma had been affected. Though long-term outcomes in thymic tumors were not improved, lymph node dissection improved the prediction of prognosis by more accurate staging (11).

In the Japanese Nationwide database, surgical results of patients with Masaoka-Koga stage III thymoma were shown to be satisfactory unless chest wall invasion was present (12).

A comprehensive analysis of thymoma-related paraneoplastic syndromes includes 507 patients from 407 publications across 59 years and 123 unique paraneoplastic disorders. Surgical resection is related to increased OS and helps achieve remission of the paraneoplastic syndrome in the majority of patients (13).

The conservation of the phrenic nerve is a crucial consideration for surgery in advanced stage thymomas, particularly in patients with severe comorbidities such as MG. The nerve-sparing method was possible in 37/140 patients with Masaoka-Koga stage III and IVa thymoma during median sternotomy surgery and allowed for suitable local control with postoperative radiotherapy (PORT) (14). Robotic-assisted operation technique can also perform adequately phrenic nerve-sparing thymectomy in selected cases of advanced thymoma (Charité database video, Video S1).

Development in non-surgical treatment options for TETs accompanying surgery should also be considered

Surgical therapy for thymic tumors with pleural involvement should select the patients and should be performed in a multimodality setting. The procedural choice depends upon the extent of tumor distribution. In 152 patients from 12 institutions over 37 years the ESTS working group found surgery-supported multimodality setting efficient for local control with excellent results regarding OS, disease-free survival (DFS), cancer-specific survival (CSS), and freedom from recurrence (FFR) (15). In certain patients, surgical cytoreduction with hyperthermic intrathoracic chemotherapy (HITOC) was possible, and the survival rates were promising (16).

Future decision making for comprehensive therapy of TETs might also include immune check-point inhibitor therapy, but their potential risk of severe autoimmune adverse events would have to be better controlled (17).

Targeted therapy for thymic malignancies is encouraging but limited by the small number of druggable genetic abnormalities that have been identified to date. Multi-targeted kinase inhibitor Lenvatinib's activity and safety research show that it might be used as a conventional therapy option for patients with advanced or metastatic thymic cancer who have already been treated (18).

In 14 patients with Masaoka stage II invasive thymoma with lesions of the thymoma capsule, intraoperative radiotherapy was proven to be safe when given locally to the tumor bed at a dosage of 10 Gy. There was no obvious increase in operation- or radiation-related complications, nor was there any effect on critical organs like the heart or lungs. Long-term effectiveness should be expected (19).

Forty-one thymomas and 49 thymic carcinomas with complete excision in stage pT3N0M0 were evaluated in a multi-institutional investigation. Adjuvant treatment for thymic cancer with superior vena cava (SVC) or innominate vein invasion was linked with increased survival, whereas lung invasion was related to poor survival (20).

The latest advances to support surgery by PORT consist of the summary of 3 publications: PORT improved the recurrence-free survival (RFS) and OS in Masaoka/Koga stage III but did not show a survival benefit in stage II in 668 thymoma patients (527 stage II and 141 Stage III) treated between 1/2000 and 12/2013 in 4 Korean hospitals (21). Patients with completely resected Masaoka-Koga stage II/ III thymoma may benefit from PORT, according to a meta-analysis of 4,746 patients from five Japanese studies (22). A phase III, open, randomized research comparing PORT to surveillance in stage IIb/III Masaoka-Koga thymoma following complete surgical resection has just begun, with 314 patients from 15 specialized French institutions expecting to have outcomes in 2028 (23).

In summary, refinements of minimally-invasive and extended operation techniques are embedded in new and improved therapeutic tools of the comprehensive treatment strategy of thymic malignancies.

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Extended Abstract

Surgical options for treatment of metastatic pleural disease: extended abstract

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Introduction

Resection of a thymic epithelial tumor with pleural metastasis is encountered in two situations, one is during a surgery for a primary stage IV tumor and the other during resection of a recurrent tumor. Various surgical procedures are used, from a simple pleurectomy to combined resection, as well as more invasive types such as extrapleural pneumonectomy (EPP). This is a review of surgical treatment options in association with other treatment modalities for thymic epithelial tumors with pleural metastases.

Surgical treatment options and outcomes

In most advanced thymoma cases, surgical treatment is adopted as a part of a multimodality treatment strategy. At our institution, the most often employed surgical technique for a highly advanced thymoma with pleural metastasis is a two-staged approach composed of a median sternotomy and posterior thoracotomy. An extended thymectomy through a median sternotomy is performed to remove the primary tumor along with as many pleural metastases as possible. The next step is a posterolateral thoracotomy with a resection of pleural metastases in the posterior thorax.

When the primary tumor shows extensive invasion of the pulmonary hilum and involves the pulmonary vessels, a pneumonectomy is required for complete resection. In such cases, an EPP procedure might be an option. Fabre *et al.* retrospectively reviewed their experiences with EPP performed for 17 thymoma patients and reported that 10-year survival was 30% (1). Wright *et al.* reported a similar outcome after an EPP (2). Those along with the report presented by Ishikawa *et al.* (3) suggested indications for an EPP for highly selected cases as well as the importance of multimodal treatment, though also emphasized a high rate of postoperative morbidity and the significance of complete resection. In author's personal opinion, EPP could be chosen only in the conditions that require a pneumonectomy for complete resection of the primary tumor.

A Japanese group reported results of a pleurectomy decortication procedure for stage IVA thymoma cases (4). That procedure was developed as an alternative to EPP as a treatment for malignant pleural mesothelioma and has recently become more prevalent. Preservation of lung parenchyma is thought to result in better quality of life for the patient and provide more opportunities for chemotherapy and radiotherapy. Reports of long-term outcomes of this novel strategy are necessary.

Several groups of surgeons have treated pleural metastases of thymoma with surgical resection in a combination with an intraoperative hyperthermic chemotherapy. Aprile *et al.* reported 27 cases, and indicated significant improvement in the local disease-free survival as compared to surgical treatment alone (5). Findings of a meta-analysis suggested the possibility of longer overall survival by use of debulking surgery as compared with a surgical biopsy (6), a notion that has been generally accepted by many clinicians because of the slow growing nature of a thymoma. Furthermore, by reducing the target lesion, other treatment options might become more effective.

A Japan Lung Cancer Society committee formed to establish guidelines for the treatment of thymic epithelial tumors examined clinical questions regarding treatment for

a stage IVA tumor and concluded (7):

(I) Multimodal treatment is strongly recommended.
(II) Surgical treatment is weakly recommended.
(III) Reduction surgery is weakly recommended.

A retrospective analysis of a database created by the Japanese Association for Research of the Thymus (JART) showed significantly better overall survival for patients with pleural metastases when macroscopic complete resection was achieved (8). In addition, overall survival was significantly higher when there were 10 or fewer pleural metastatic lesions. Presumably, the group with 11 or more included those with numerous metastases, for which complete resection cannot be achieved. Nevertheless, an important finding was that patients with incomplete resection still achieved an overall survival over 10 years in nearly 50% of cases, demonstrating the clinical significance of reduction surgery for thymoma with pleural metastases.

Characteristics of pleural metastases and indications for surgery

It is important to take into account the characteristics of pleural metastases before performing treatment for an affected case. The metastatic lesions vary in size, number, degree of invasion of thoracic structures, and pathology of the primary tumor. A case with a few small lesions has a good chance of cure by surgery alone, whereas a more advanced condition seems difficult to be treated only by surgery and it likely requires a multimodal strategy. When resecting the diaphragm, spreading of neoplastic cells into the peritoneal cavity should be avoided. It is recommended that the chosen treatment strategy should be determined based on the metastases characteristics. A common system to describe the size, number, location and grading of invasion of the pleural metastases is required for further investigation.

Surgical treatment for recurrence in pleura

The JART database includes details of 420 patients with tumor recurrence, of whom 162 underwent re-resection. In the surgical treatment group, 75% were thymoma cases, and more than half of the resected lesions were metastases to the pleura or pericardium. Complete resection of the thymoma resulted in a 10-year survival noted for 75% of cases (9). All types of metastases were included in that group and long-term survival was not limited only to pleural metastases cases, but a good outcome following resection of pleural metastases is expected when a surgical operation is feasible.

Conclusions

The effectiveness of surgical treatment alone for thymoma pleural metastases is limited to highly selected cases, for example, those with a small number of lesions. Surgery should be generally considered as one of the most effective method and part of multimodal treatment. A variety of conditions are found in cases of thymic epithelial tumors with pleural metastases and use of a surgical procedure should be determined depending on the condition of the metastatic lesions.

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