Review Article

Mediastinal germ cell tumors: a narrative review of their traits and aggressiveness features

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Objective: Mediastinal extragonadal germ-cell tumors (MEGCTs) are rare neoplasms with a multifaceted clinical behavior. This paper is devoted to review their main characteristics, including histological patterns and different factors of aggressiveness in MEGCTs. Proper understanding of the latter can help to better stratify patients' prognoses and improve clinical management.

Background: Different theories exist on the origin of MEGCTs, including primordial germ cells deposition during embryogenesis. MEGCTs predominantly affects young males and aggressiveness follows the ability of local and systemic spread of each germ-cell neoplasia subtype, as well as their distinct responsiveness to therapy. Indeed, non-seminomatous MEGCTs have a worse prognosis. Unfortunately, they are also more frequent than seminomas in the mediastinum. Regardless of histological type, local aggressiveness can follow tumoral expansion with compression on or infiltration of mediastinal structures. Chemotherapy can be effective in reducing neoplastic volume, but different levels of sensitivity can be found in different MGCTs. In particular, a chemo-resistant teratoma component of a mixed MEGCTs can undergo a paradoxical enlargement after chemotherapy, while other components of the tumor regress. This is reflected by a concomitant normalization of serum tumoral markers and cardiopulmonary deterioration due to compression. Such clinical phenomenon, called growing-teratoma syndrome (GTS), requires a prompt surgical approach.

Methods: A literature research of pertinent epidemiological, pathological and clinical articles was conducted.

Conclusion: The mediastinum can harbor different kinds of neoplasia, including GCTs. The full spectrum of MEGCTs includes a variety of tumors with different clinical behaviors. Aggressiveness follows the inherent ability of local and systemic spread of each neoplastic type, as well as their distinct responsiveness to therapy.

Keywords: Mediastinum; germ-cell tumor (GCT); aggressiveness; prognosis

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Introduction

Germ-cell tumors (GCTs) are neoplasms that can arise within the gonads (i.e., testicles and ovaries) or at extragonadal sites, where they are referred as extragonadal germ-cell tumors (EGCTs). Among the latter, midline areas of the body are typically affected (1), especially the mediastinum (2). This tendency could be explained by considering EGCTs as derived from primordial germ

cells deposited during migration from the epiblast to the genital ridge during embryogenesis (3). Still, extra-midline cases have been reported [e.g., lungs (2) and kidneys (4)] and some challenge the existence of bona fide EGCTs which they consider to be metastases. The debate is fueled by the presence of non-random chromosomal changes essentially identical to the ones present in gonadal GCTs (5). Abnormalities of 12p chromosome are the most specific both at gonadal and extragonadal sites (6). By some authors this could suggest a gonadal origin of EGCTs, with an early migration of neoplastic cells to extragonadal sites (5). Still, despite the presence of some biological overlaps with gonadal GCTs, mediastinal EGCTs (MEGCTs) not only stand out for their peculiar location. They as well have distinct epidemiological features, worth-noting histological patterns and factors of aggressiveness related to their growth within specific anatomical site and the structures therein present. We present the following article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-21-22/rc) and on the base of a literature search of case reports, epidemiological surveys, clinical and pathological studies written in English with no specific time-frame considered.

Epidemiology

EGCTs are rare neoplasms whose total crude incident rate is 1.27/1,000,000 person-years, peaking between 15 and 24 years of age at 2.2/1,000,000 person-years (2). Such increased amount of cases around the onset of puberty is considered to reflect a hormone-related growth boost of neoplastic germ-cells (3). The mediastinum is the most frequent location of EGCTs (2,3), especially in the anterior compartment, although involvement of the middle mediastinum has also been reported (7,8). Still, MEGCTs constitute only 1–3% of germ cell malignancies (7) and 16% of mediastinal tumors (9). MEGCTs predominantly affect males (3) and patients have a 10% chance of developing metachronous testicular cancer over a 10-year period (10,11). Individuals affected from Klinefelter syndrome are especially at risk and the presence of this syndrome should be investigated among young patients with MEGCTs (12). Women are instead less frequently affected by MEGCTs and they usually, but not exclusively, present with yolk sac tumors (YSTs) or mature teratomas (MTs) (13-16). The latter are actually the most frequent type of MEGCTs in men as well. In fact, non-seminomatous neoplasms represent up to 85% of MEGCT, prevailing over mediastinal seminomas (3,10,17). This picture also applies to individuals suffering from Klinefelter syndrome (12) and it contrasts with testicular pathology, where seminomas outnumber non-seminomatous neoplasms.

Histological patterns and factors of aggressiveness

MEGCTs have in general a worse prognosis compared to their gonadal counterparts (18). Nevertheless, not all MEGCTs are equal and different features can be identified in the modulation of aggressiveness.

Type of MEGCT

According to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification of prognostic groups for patients with GCTs, MEGCTs are classified in the poor-prognosis class (i.e., 50% 5-year survival rate) (18). Nevertheless, this projection can be considered accurate for non-seminomatous MEGCTs, whereas mediastinal seminomas have a much better prognosis which parallels intermediate- and good-prognosis IGCCCG classes (18,19). Also, mediastinal seminomas respond very well to chemotherapy and radiotherapy with excellent long-term chances of cure (19), while non-seminomatous MEGCTs require chemotherapy followed by surgical resection of the residual tumor (20). It must be also remembered that MEGCTs can feature more than one type of germ-cell neoplasia within a single tumor (i.e., mixed MEGCT). Acknowledgment of each present entity is of paramount importance for patient management and cannot be overstressed.

Mediastinal seminomas show discohesive epithelioid cells with clear cytoplasm, distinct cellular membranes and nucleoli. These cells have a CD117+ immunohistochemical phenotype, which could be a potential diagnostic pitfall in the differential diagnosis with thymic carcinoma. Intratumoral lymphocytic infiltrates and granulomatous reactions can become very prominent, up to the point of significantly obscuring the underlying neoplasia. Scattered multinucleated syncytiotrophoblast can be found within seminomas, without implying a diagnosis of choriocarcinoma. The latter would require the concomitant presence of multinucleated syncytiotrophoblast and mononucleated cytotrophoblast. YSTs can have different pattern of growth, the most frequent being microcystic/reticular, with or without Schiller-Duval bodies. However, choriocarcinoma and YST can be diagnosed even without

performing a tumoral biopsy by detecting high blood levels of human chorionic gonadotrophin (hCG) and a-fetoprotein (AFP), respectively (20).

MTs don't feature elevated tumoral markers instead and they therefore require a biopsy to be diagnosed (20). Moreover, they are chemo-resistant and they require a surgical approach (20). Histologically, mature forms show only phenotypically—developed tissues derived from one of the three germinal layers (e.g., skin with cutaneous adnexa, teeth, bone and cartilage). MTs often have cystic areas that can be so prominent to radiologically imitate pleural and pericardial effusions (21,22). Three major factors of aggressiveness can be present in teratomas: digestive tract tissue, neuroectodermal immature cells and somatic malignant transformation (SMT). Digestive tract tissue capable of secreting proteolytic enzymes (e.g., pancreatic glands) not only makes MTs more prone to rupture, but it can also erode mediastinal structures (23). Neuroectodermal immature components are identifiable as small blue cells with S100+ immunophenotype. As they can be focal (24), collection can be missed in biopsies. Not only the presence or absence of immature tissue could be important, as a grading system has been developed in the ovary on the basis of the quantity of immature neuroepithelium (25). According to it, the larger the amount of immature neuroepithelium, the worse the prognosis (25), but this has not been validated in the mediastinum (24). Moreover, some authors suggested that immature teratomas, if radically resected, could still be associated to a prognosis which is equivalent to that of a MTs (26).

SMT is defined as the presence within GCTs of non-germinal malignant tumors (i.e., carcinomas and sarcomas). These can include adenocarcinoma, rhabdomyosarcoma, neuroblastoma as well as many other phenotypes which retain their proper morphological and immunophenotypical features (27,28). Nevertheless, differently from the corresponding neoplasms outside the context of GCTs, somatic malignant components often carry 12p chromosomal alterations, paralleling germinal neoplastic cells and aiding in the differential diagnosis with metastases (29). SMT in the form of adenocarcinoma must also be distinguished from embryonal carcinoma, which is the least frequent MEGCT and it can be made of glandular structures with atypical epithelioid cells (30). Ancillary immunohistochemical staining would prove positive for CD30 and OCT3/4 in the case of embryonal carcinoma, while NST would mark positive for different markers according to the phenotype (e.g., CDX2 in colonic-type adenocarcinoma). In contrast with cases of gonadal GCTs, patients suffering from MEGCTs have also an increased risk of developing hematological neoplastic diseases, especially acute megakaryoblastic leukemia (AMKL) (31). Malignant hematological cells have indeed been found within MEGCTs (32) and the source of hematopoietic malignancies might be represented by precursor cells within YST components (33). Still, AMKL usually presents as a bone-marrow involvement. Nevertheless, MEGCTs with concomitant AMKL have been found to share mutations in p53 and PTEN genes, as well as the presence of isochromosome 12p (i12p) (34-36). These data supports that these tumors share a common founding clone, as well as the importance of such genetic alterations in the pathogenesis of these associated tumors that might represent a unique biological entity when they co-occur (34-36).

Compression and infiltration of mediastinal structures

MEGCTs can become clinically worrisome by means of their growth patterns. Even when they do not have infiltrative margins, but rather an expansive profile, they can get big enough to compress on mediastinal structures leading to a variety of possible clinical presentations. Pressure on major vessels can impair blood flow. If the superior vena cava is involved and compression develops quickly, a superior vena cava syndrome can ensue, bringing to a medical emergency (37,38). If the process is slower, flows through the azygos system or the inferior vena cava can (at least temporarily) compensate for the obstruction (37). Pressure on the microvasculature can instead bring to tissue necrosis. For instance, ischemic death of the bronchial wall would lead to perforation of the airway with hemoptysis (39-41). Rupture of a teratoma within the airways has been also reported to cause the expectoration of tumoral hair (trichoptysis) even in the absence of blood (23). Other reported presentations are dyspnea, Horner syndrome and cardiac arrythmia following pulmonary, nervous and right atrial compression, respectively (21,30,42,43).

Contact between MEGCTs and mediastinal structures can be furtherly complicated by fibrotic bands which create adherence or by an infiltrating growth pattern of neoplastic cells. In such cases, radical surgical treatment is either reached by en-bloc removal of encroached organs along with the tumor, or not possible altogether, considering the unresectable vital anatomical structures present in the mediastinum (8,37,38,40,44).

Response to treatment

As previously mentioned, patients with MTs can be successfully treated with surgery, if feasible. Nevertheless, this also reflects the resistance of MTs to chemotherapies. Such biological feature can become problematic after a patient have received systemic therapy for a non-seminomatous MEGCT with a teratomatous component. The latter can be selected, surviving to the treatment and starting to grow. This leads to the so-called growing-teratoma syndrome (GTS). GTS is clinical phenomenon set before or immediately after the fourth cycle of cisplatin-based chemotherapy with a paradoxical enlargement of the tumor, concomitant normalization of previously elevated serum tumoral markers and cardiopulmonary deterioration caused by compression of the great vessels/heart/lungs (45). GTS therefore requires a prompt surgical approach (45,46). Pathology reports usually tell of teratomatous elements in a setting of inflammation and necrosis (46). Although the prognosis of GTS is considered to be excellent after the excision of the tumor (47), there are reports of relapses even after complete resection (i.e., absence of residual masses at the end of the surgical operation and at postoperative CT scan) (48) Further research is therefore needed to optimize an effective therapeutic approach to this complication, a possibility limited by its rarity.

Conclusions

The mediastinum can harbor different kinds of neoplasia, including GCTs. The full spectrum of MEGCTs includes a variety of tumors with different clinical behaviors. Aggressiveness follows the inherent ability of local and systemic spread of each neoplastic type, as well as their distinct responsiveness to therapy.

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Footnote

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