Mediastinal seminoma in the setting of advanced colorectal cancer: beware atypical sites of metastasis

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Abstract

Primary mediastinal seminoma is an uncommon malignant extragonadal germ cell tumour of the anterior mediastinum occurring almost exclusively in men. We report a case of mediastinal seminoma with prominent follicular lymphoid hyperplasia in a patient with metastatic colorectal cancer and discuss diagnostic considerations including prominent secondary change, immunohistochemical analysis and differential diagnosis.

Keywords extragonadal germ cell tumour; immunohistochemistry; mediastinal seminoma; mediastinum; thymus

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Case report

A 54 year old male presented for preoperative workup following a recent diagnosis of primary rectal carcinoma with biopsy proven lung metastases. PET/CT imaging demonstrated an incidental FDG avid nodule (SUV 3.8) in the anterior mediastinum which was considered an atypical site for colorectal metastatic disease (Figure 1). Serology revealed elevated baseline CEA (CEA = 13 (ULN <5)) while all other biochemical parameters and tumour markers were within reference range. Diagnostic excision with intraoperative sampling for culture and sensitivity was performed. Macroscopic evaluation revealed a marginated, non-encapsulated 13mm nodule present within adipose tissue. Histology showed marked lymphoid hyperplasia with reactive germinal centre formation replacing fat lobules within which a discrete population of intermediate to large cells was observed in small clusters and singly dispersed (Figure 2). The tumour cells were embedded in a meshwork of proliferated thymic epithelium with admixed tendrils of fibroconnective tissue. The cells were characterized morphologically by indistinct cell membranes, pale/clear vacuolated cytoplasm, round nuclei with open nuclear chromatin and prominent macronucleoli. There was extensive background sclerosis with foreign body type giant cell reaction and non-caseating granulomata. Immunohistochemistry revealed that the lesional cells co-expressed OCT4 and PLAP (Figure 3). A pathological diagnosis of mediastinal seminoma with florid follicular lymphoid hyperplasia was made and subsequent investigation for occult gonadal disease proved negative. The patient proceeded to definitive surgery and at three year follow up remains free of disease.

Discussion

The mediastinum is an anatomic compartment delimited by the thoracic inlet and the diaphragm which serves as a conduit for vital intrathoracic structures. Extragonadal germ cell tumours (EGCTs) arise most frequently at this site where they comprise approximately 15% of all primary mediastinal neoplasia in adults.[1] Arrested migration of primordial germ cells from the proximal epiblast to the genital ridge and aberrant localization to midline structures during embryogenesis has been put forward as a mechanistic pathway for the origin of extragonadal germ cells. It is thought that ectopic germinal elements may subsequently undergo malignant transformation. Limited available molecular data from CGH appear to show biologic homology particularly in regard to chromosomal imbalance between gonadal and extragonadal germ cell tumours suggesting a common pathogenetic origin.[2] Rarely, metastasis from a regressed primary gonadal GCT may be considered in extracranial sites outside the mediastinum and retroperitoneum.

Primary mediastinal seminoma (PMS) is a primary malignant germ cell tumour of seminomatous germ cells of the thymus and the second most common EGCT after mature teratoma. Typically patients are young adult males who present with a bulky anterior mediastinal mass, compressive symptoms as well as mildly elevated β-hCG. Marked elevation of serum tumour markers (β-hCG >1000 IU/L) usually indicates the presence of non seminomatous elements.[3] While Klinefelter syndrome and unusual

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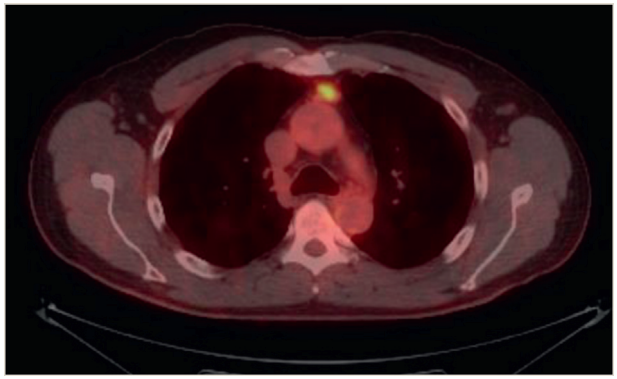

Figure 1 Fluorodeoxyglucose (FDG)-PET CT axial section showing FDG avid enhancing soft tissue mass within the anterior mediastinum. (PET, Positron Emission Tomography).

haematological neoplasias including clonal megakaryocytic disorders have been associated with NS-EGCTs, no such biologic associations are known to exist in PMS.

Microscopic findings are indistinguishable from testicular tumours and frequently consist of cellular sheets of intermediate to large cells, sometimes displaying a more subtle nested growth pattern with glycogenated clear to eosinophilic cytoplasm, indistinct cell membranes, rounded nuclei and prominent nucleoli. The neoplastic infiltrate is separated by thin fibroconnective septations and frequently embedded in a marked inflammatory cell infiltrate rich in small lymphocytes. Secondary change including non-caseating granulomata, trophoblastic giant cells, remnant thymic tissue and cystic degeneration may feature prominently and on occasion obscure morphologically classic cells raising the spectre of other more common mediastinal pathology including multilocular thymic cyst and lymphoproliferative disease, including Hodgkin lymphoma.[4] The prominent nested architecture can closely simulate neuroendocrine tumours and inadequate fixation may give rise to artefactual cellular discohesion closely resembling embryonal carcinoma. In these settings immunohistochemistry is useful in demonstrating a seminomatous germ cell immunophenotype. OCT3/4 shows strong nuclear labeling in tumour cells while CD117 typically displays membranous positivity.[3] Cytoplasmic PLAP staining is found in approximately 50% of cases, less commonly than in gonadal tumours. Low molecular weight keratin more often demonstrates a characteristic paranuclear dot like staining pattern than in its testicular counterpart. Intracytoplasmic glycogen is highlighted by PAS, particularly in tumours with prominent clear cell morphology.

As in testicular pathology, distinction between seminomatous and non seminomatous tumour entities is crucial for appropriate risk stratification and to direct clinical therapy. Seminomas are exquisitely sensitive to radiation therapy and single agent platinum-based chemotherapy. The presence of any non-seminomatous tumour component qualifies for designation as a non seminomatous EGCT, which parallel management principles in urologic oncology.

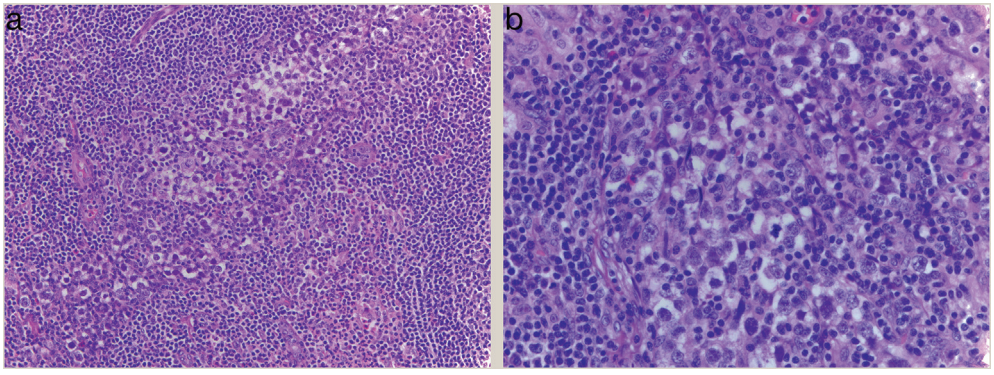

Figure 2 a, Neoplastic seminomatous cells embedded in a rich lymphoid stroma with hyperplastic follicles (H&E, original magnification: x10). b, Loose nested growth of morphologically classic seminomatous tumour cells showing prominent cytoplasmic clearing, rounded nuclei separated by tendrils of fibroconnective tissue (H&E, original magnification: x40).

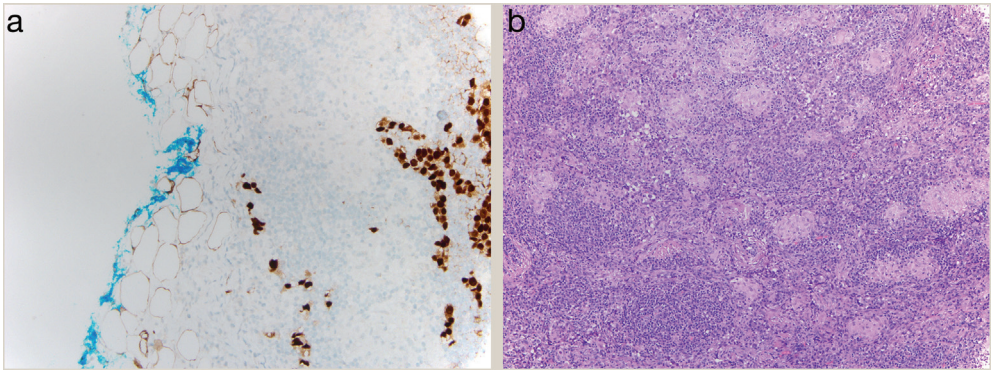

Figure 3 a, Strong nuclear labelling of tumour cells with OCT4 immunohistochemistry (OCT4, original magnification: x20). b, Non caseating granulomatous inflammation (H&E, original magnification: x40).

Although survival outcomes in PMS are superior to NS-EGCTs, locally advanced tumours are frequently asymptomatic and metastatic disease is seen at presentation in approximately 40% of patients.[5,6] Nevertheless overall survival rates of between 88 and 100% can be achieved with aggressive chemo-radiotherapy protocols.

In summary, PMS is an uncommon EGCT with a strong male predilection and microscopic features indistinguishable from testicular seminoma frequently accompanied by prominent secondary change. When reviewing cystic, granulomatous or lymphocytic rich inflammatory lesions of the anterior mediastinum in men in which an obvious tumour cell infiltrate is not apparent consideration should always be given to a paucicellular or undersampled PMS. In addition, atypical sites of metastases warrant detailed investigation to exclude the possibility of synchronous double primary tumours. ◆

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Practice points

- Mediastinal seminoma is an uncommon malignant tumour of extragonadal seminomatous germ cell origin occurring in the anterior mediastinum of men.
- While the classic histomorphologic features are indistinguishable from testicular tumours, mediastinal seminoma is frequently accompanied by secondary change including a rich lymphoid stroma, granulomatous inflammation and cystic degeneration which can obscure the tumour cell infiltrate.
- Tumour cells express a germ cell phenotype including OCT4 and CD117. Cytoplasmic staining for PLAP is seen less commonly than in testicular tumours. LMWK produces a characteristic paranuclear dot like staining profile in a subset of cases. PAS histochemistry can be used to highlight intracytoplasmic glycogen.
- Unusual sites of metastases in colorectal cancer merit detailed investigation to exclude the possibility of a second primary tumour even in the absence of elevated serum tumour markers.

Self-assessment questions

1. Which of the following is the most common malignant extragonadal germ cell tumour?

A. Immature teratoma
B. Mature teratoma with somatic type malignancy
C. Mixed germ cell tumour
D. Mature teratoma
E. Embryonal carcinoma of the mediastinum

Answer D. Mature teratoma is the most common extragonadal germ cell tumour followed by mediastinal seminoma.

2. A previously well 35 year old man presents with a short history of dry cough, dyspnea and facial swelling. LDH was mildly elevated and serum β-hCG and AFP were within normal limits. CT imaging demonstrates an 8cm anterior mediastinal soft tissue mass with pretracheal lymph node enlargement and a right pleural effusion. Histologic evaluation of the excision material reveals sheets of neoplastic cells, separated by thin strands of fibrous tissue displaying moderate amount of lightly eosinophilic cytoplasm, rounded nuclear contours and prominent central nucleoli. The presence of focal multinucleated syncytiotrophoblast cells is noted. A broad immunohistochemical panel is performed which shows lesional cell positivity for CD117 and PLAP. HCG and GATA3 highlight multinucleate syncytiotrophoblasts. What is your diagnosis?

A. Choriocarcinoma of the mediastinum
B. Mixed germ cell tumour of the mediastinum
C. Primary mediastinal seminoma
D. Metastatic choriocarcinoma

Answer C. The presence of focal multinucleated syncytiotrophoblasts is an uncommon secondary feature seen in 5–10% of mediastinal seminomas. Mediastinal choriocarcinoma is the least common germ cell tumour of this site and diagnosis require cytotrophoblast and syncytiotrophoblast elements and is typically characterized by marked cellular pleomorphism. Extensive sampling is required to exclude the more common mixed germ cell tumour.