Case Report

Metastatic Testicular Mixed Germ Cell Tumors. A Diagnostic Dilemma in Cytology

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ABSTRACT

Germ cell tumours (GCTs) are the most common malignant tumours of the testes. Metastasis to cervical lymph nodes as the initial manifestation is rare. Mixed GCTs are a diagnostic challenge to the pathologist, particularly in cytology because of their histologic diversity; more so when they occur at unexpected sites, with unknown primary. Two young adult males presented with enlarged cervical lymph nodes. Fine needle aspiration cytology (FNAC) was reported as metastatic undifferentiated carcinoma, suspected to be arising from testis. Subsequently, left testes were found to be enlarged in both; histopathological examination confirmed mixed GCT. GCTs are important differential diagnoses for metastatic undifferentiated carcinomas in cervical lymph nodes in young adult males. A reliable diagnosis can be made on cytology, even in those patients in whom the primary is not known. This study aims to highlight the cytologic hallmarks of metastatic mixed GCT to arrive at an accurate diagnosis.

***Key words**: Fine needle aspiration cytology, metastasis, unknown primary, mixed germ cell tumour*

INTRODUCTION

GCTs account for 1% of all neoplasms in males and 98% of malignancies in the testes. Rarely, these tumours present as cervical lymphadenopathy with an occult primary. Rapid and accurate diagnosis is essential, as it has therapeutic and prognostic implications. FNAC is an accepted procedure for their diagnosis at metastatic sites, unlike primary tumours in the testis. Mixed tumors constitute 40-45% of all primary GCTs.[1] They pose a diagnostic challenge to the pathologist, considering their histologic diversity and differential diagnosis at various sites of metastasis. It is one of the differential diagnoses for metastatic carcinoma in a lymph node and tends to be ignored in Asian countries, where it is relatively rare. Metastatic carcinoma carries a poor prognosis compared to the potentially curable GCT, even when disseminated. Therefore it is important for the pathologist to recognise and alert the clinician to such a possibility.[2] Very few case series on cytologic features of GCTs at extra gonadal sites are reported in literature.[3] The cytomorphologic features of metastatic mixed germ cell tumours in cervical lymph nodes are described here.

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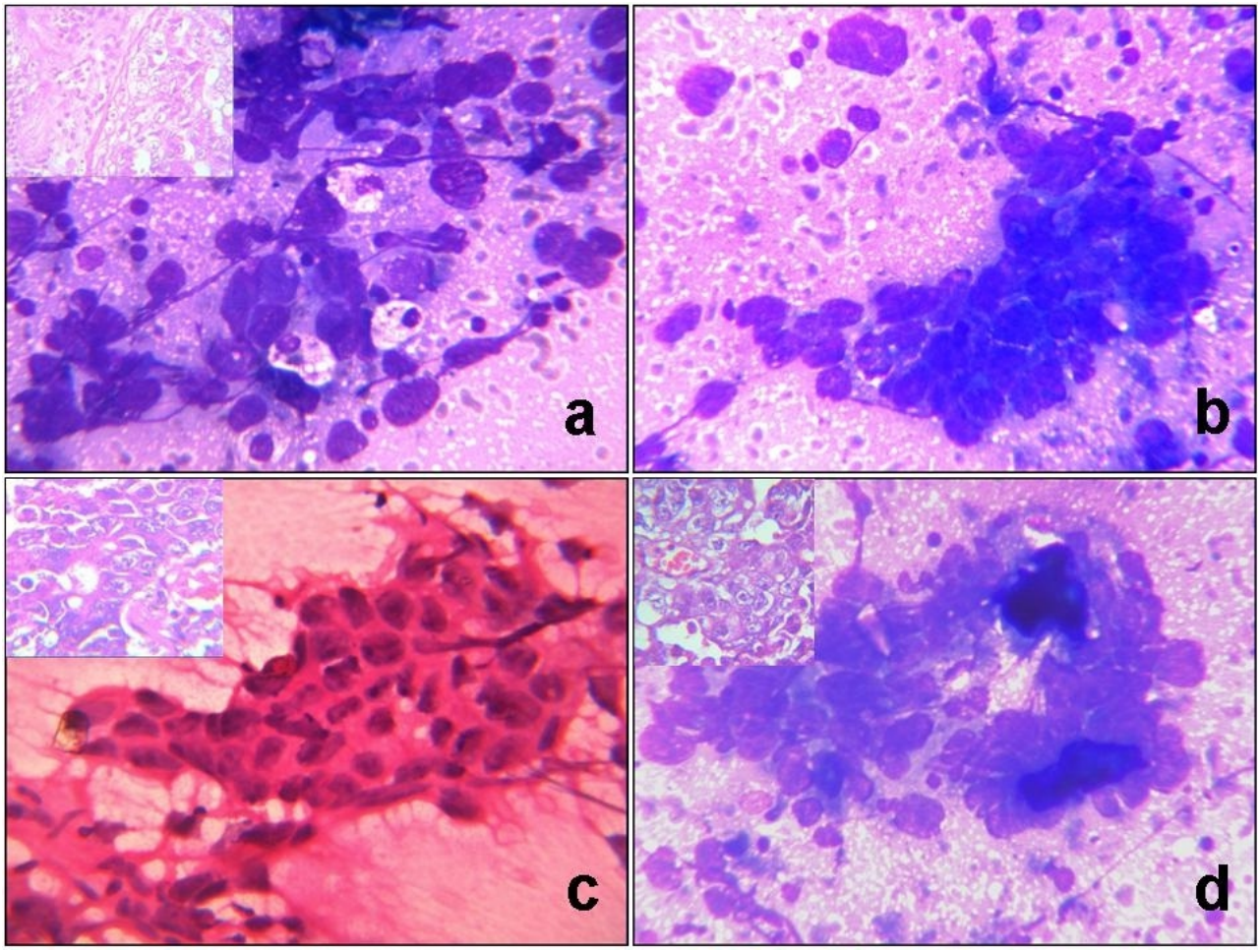

Fig 1a: FNA smear from an area of seminoma is cellular, composed of discohesive population of large, round malignant cells and lymphocytes in a tigroid background (Giemsa, 40x) [Inset-tissue section, H&E, 40x]

Fig.1b: Air-dried smear from a focus of embryonal carcinoma showing a cohesive cluster of malignant cells with scant cytoplasm and pleomorphic nuclei (Giemsa, 40x)

Fig.1c: Smear from a focus of embryonal carcinoma consisting of syncytial aggregate of irregular shaped nuclei, some with prominent nucleoli (H&E, 40x) [Inset-tissue section, H&E, 40x]

Fig.1d: Aspirate smear from an area of yolk sac tumor showing metachromatic basement membrane-like material within a cell cluster (Giemsa, 40x) [Inset-tissue section, H&E, 40x]

Case report

Case 1

A 27 year old male presented with history of fever and enlarged left supraclavicular and cervical lymph nodes. FNAC was done from multiple areas; smears were stained with Hematoxylin and Eosin stain and Giemsa. Smears were markedly cellular, composed of malignant cells scattered discohesively, arranged in loose clusters and focal acinar patterns. The tumour cells were large, with scant to moderate eosinophilic cytoplasm and large, pleomorphic nuclei with one or more prominent nucleoli (Figs. 1a, 1b). Occasional bi- and multi-nucleate tumor cells were noted along with a few mitotic figures. Numerous small lymphocytes were seen admixed with the tumor cells. Necrosis was seen in the background in some smears. A cytologic diagnosis of metastatic poorly differentiated carcinoma was made. The clinician was advised to look for primary in the testis. Further examination revealed a hard mass in the left testis, measuring 5x5cms. Retrograde left orchidectomy with left cervical and supraclavicular lymph node excision was done. Histopathological examination confirmed mixed germ cell tumor of testis, with predominant embryonal carcinoma and seminoma components, metastatic to left supraclavicular and cervical lymph nodes.

Case 2

A 32 year old male presented with enlarged left lower cervical lymph nodes. Multiple aspirations were done with a fine needle. Air dried and fixed smears were stained with Giemsa and H&E respectively. The smears were highly cellular, composed of large cells, dispersed singly and arranged in papillary formations (Figs.1c,1d). The cells had moderate eosinophilic or finely vacuolated cytoplasm. The nuclei were large, vesicular with 1-3 prominent nucleoli. Numerous lymphocytes were seen with scattered multinucleated giant cells and mitotic figures. Haemorrhage and necrosis were noted in some smears. With our previous experience, the possibility of metastatic germ cell tumor was raised. On further examination, a tumor was detected in the left testis, measuring 4x3cms. Serum assays showed raised alpha-fetoprotein (AFP) and human chorionic gonadotropin (β-hCG). Left high inguinal orchidectomy was done with left lower cervical lymph node excision. Histological examination confirmed mixed GCT of testis, with metastasis to left cervical lymph nodes. The tumor was composed of seminoma, embryonal carcinoma (EC), yolk sac tumor (YST) and a focus of choriocarcinoma.

DISCUSSION

GCTs are common in the testis. About 5% involve supraclavicular and cervical lymph nodes; it is the first clinical manifestation in 5% of cases. [4] They have a predilection for young adults, with peak incidence in the late twenties and thirties.[5] The age distribution suggests an initiating event in the prenatal period, allowing the tumor to grow until adolescence.[4] Genetic and environmental factors play a role, as suggested by distinctive geographical and racial incidence. It is more common in the west than in Asia; highest incidence is seen among white men in northern Europe.[2,5] Irrespective of the geographic distribution, pathologists must be aware of this entity, as it is potentially curable. A

missed diagnosis can be of serious consequence.

GCTs are categorised as seminomas and non seminomatous germ cell tumours (NSGCT). Most NSGCTs contain two or more components and are classified as mixed germ cell tumours. They are aggressive tumours, comprising about 10% of testicular neoplasms.[4] Most of them present as painless testicular mass. A greater propensity for distant metastasis is seen in tumours with high-risk histology, such as choriocarcinoma.[6]Testicular tumours carry excellent prognosis: most patients, including those with disseminated disease, respond well to modern therapy and are potentially curable. This is facilitated by early diagnosis and thorough work- up for staging.

The role of FNAC is well established in the diagnosis and staging of metastatic GCTs.[1] A high index of suspicion is required for its diagnosis; it is often misinterpreted as undifferentiated carcinoma. Diagnosis of NSGCT is more challenging because of its varied cellularity and the broad spectrum of differential diagnosis. Young age of the patient is an important clue. Metastases usually reflect the histology of the primary tumor. Accurate sub classification into seminomatous or nonseminomatous germ cell tumor is important to determine the treatment.

Seminoma shows characteristic features on cytology: the smears are cellular, comprising a homogeneous population of large, atypical cells dispersed singly and in loosely cohesive clusters. The cells have fragile, vacuolated but well defined cytoplasm. Nuclei are large and round, each with a single prominent nucleolus. A distinctive tigroid (lace-like) background may be seen in some and lymphocytes are a prominent feature in most smears. Lack of tigroid background does not exclude seminoma, and neither is its presence pathognomonic of this entity.[1,7] Gentle smearing techniques are suggested to prevent cell distortion and shearing of cytoplasm, which makes diagnosis difficult. Immunostains on cell block sections help differentiate seminoma (OCT 3/4+, CD117+, PLAP+ and LCA-) from neoplasms that show discohesive pattern on cytology, including adenocarcinoma (OCT3/4-, EMA+), melanoma (OCT3/4-, S-100+, HMB-45+) and lymphoma (OCT3/4-, LCA+).[1,5,7]

Aspirates from EC show highly cohesive clusters of large, anaplastic cells, with scant ill-defined cytoplasm. The cells in these clusters lack cell borders, forming syncytial tissue fragments. The nuclei are large and pleomorphic. Bi- and multi-nucleation is common. It should be considered in the differential diagnosis of metastatic poorly differentiated carcinoma in young adult males. History of testicular GCT, serum markers (AFP, β-hCG) and immunostains (OCT 3/4+, PLAP+, EMA-, CD30+) are usually required to make a definitive diagnosis. [1,2,3,5,7]

Smears from YST are moderately cellular, with tumor cells arranged in sheets, loose groups, cell balls and complex architectural patterns. Tumor cells have abundant, vacuolated cytoplasm, vesicular nuclei with prominent nucleoli. Presence of metachromatic basement membrane-like material and mesenchymal fragments is consistent with cytologic diagnosis of YST.[1,3] Intracytoplasmic hyaline globules and Schiller-Duval bodies are seen in few cases.[3] Serum markers (AFP, α1AT) and immunostains (AFP+,

OCT 3/4-) help differentiate YST from seminoma, when cells show a discohesive pattern.[1,5]

Loose groupings of syncytio- and cytotrophoblasts are characteristic of choriocarcinoma. Multinucleate syncytiotrophoblastic giant cells are seen in other mixed GCTs and carcinomas at various sites.[2,7] They are large cells with abundant cytoplasm, bizarre cytoplasmic processes and large polymorphous nuclei. They are positive for β-hCG, α- inhibin and EMA. Cytotrophoblasts, more typical of choriocarcinoma, are polygonal cells, with basophilic cytoplasm, eccentric nuclei and distinct nucleoli.[8]

Review of smears from the two cases described here, showed cytologic features of mixed germ cell tumor with seminoma and embryonal carcinoma components (Fig. a, b, c). Smears from the second case also showed metachromatic basement membrane-like material amidst acinar structures, consistent with yolk sac tumor (Fig. d). Syncytio- and cytotrophoblasts could not be identified in the smears. A diagnosis of metastatic GCT was inferred in both the cases; however, subtyping was not attempted on aspiration smears.

An inability to make a confident diagnosis of metastatic mixed GCT on cytology is reported in many studies.[3,8] This is attributed to limitations in sampling, poor display of some components, and overwhelming presence of one component.[8] These can be overcome by adequate sampling, a thorough search for other components and correlation with serum tumor markers.[3] Mixed GCT should be considered in all those cases where more than one pattern is observed in smears. However, it is a possibility in all patients in whom metastatic GCT is diagnosed on cytology. Immunostaining should be done on sections from cell blocks whenever possible. It plays an important role in the diagnosis of metastatic GCTs, reflecting the differentiation of the germ cell component.[1,9] Adequate treatment includes surgery, chemotherapy and radiotherapy, alone or in combination.

CONCLUSION

FNAC is a rapid and reliable technique for the diagnosis of GCTs at extragonadal sites. Metastatic mixed GCTs pose a significant problem because of their histologic diversity and variations in sampling. This is particularly so when lymph node metastasis is the only presentation, where the differential diagnostic possibilities are wider. It is imperative for pathologists to be familiar with their cytologic features as a correct diagnosis could mean complete cure for the patient with current treatment modalities. Even in cases where a definite diagnosis cannot be made on cytology alone, it offers clues to the possibility of GCT. This reinforces the need to consider metastatic germ cell tumor in the differential diagnosis in young adult males presenting with cervical lymphadenopathy. Cell blocks made from additional samples are useful for ancillary techniques like immunocytochemistry.

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