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AN INTERESTING CASE OF MALIGNANT THYMOMA - A CASE REPORT

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Abstract :
Primary tumors of thymus are uncommon and accounts for less than 1percent of all neoplasms. Thymomas and Lymphomas are the commonest primary tumors .A case of 45 year old male presented with features of difficulty in breathing for the past 7 months. Investigation revealed lobulated heterogeneous mass in anterior mediastinum. Guided FNAC was done and was suggestive of Thymoma. Surgical resection of the mass could not be done due to invasion to adjacent organs. Histopathological examination of biopsy showed features of Invasive Malignant Thymoma-Type B3 and Type A.Hence this case is reported for its rarity by histopathological classification.

Keyword :

Thymoma, Thymic epithelial tumor.

INTRODUCTION:

The thymus is located in the anterior mediastinum and is derived embryologically from the third and to a minor degree, the fourth pharyngeal pouch. [10, 11].It is a bilobed organ enclosed in a thin fibrous capsule .

Histogenesis:

Thymus is a lymphoepithelial organ,essential for T-lymphocytes maturation[10].It comprises of endodermally derived epithelial cells and bone marrow derived lymphocytes[9]. The dark stained cortex is densely populated by lymphocyte (thymocyte) and light stained medulla where lymphocytes are less densely populated. Interconnecting meshwork of epithelial cells form the scaffolding and are the milieu of lymphocytes. Interspersed perivascular spaces are also present. The epithelial cells in the cortex are polygonal with abundant cytoplasm and ovoid vesicular nuclei and in the medulla it is spindle shaped with scanty cytoplasm. [11]. It also forms Hassal corpuscles with concentric keratinisation[10].

Immunohistochemistry of normal thymus:

Epithelial component:These are best highlighted by cytokeratin, predominantly by their multiple delicate .

cytoplasmic processes
Lymphoid component: The cortex expresses TdT,Cytoplasmic CD3,CD1a , CD99a and high proliferative index. Medullary thymocyte are positive for both surface and cytoplasmic CD3 but negative for TdT, CD1a, CD99a. [10].

Tumors of thymus:
It accounts for less than 1% of all neoplasms [13] .
Primary tumors comprises of :
Epithelial tumors,Neuroendocrine tumors, Germ cell tumors Etiology is unknown and the biology is complex.[13] .Primary tumors of thymus are uncommon. The commonest primary tumors are thymoma and lymphoma. Less common are the Germ cell tumors which show better prognosis. The spectrum of epithelial tumors comprises of encapsulated thymoma, invasive thymoma and thymic carcinoma[10].
Thymoma exhibits organoid features, with lobulation filled with cytologically bland neoplastic thymic epithelial cells [4] accompanied by reactive lymphoid cells[4,10].All are potentially malignant. It occurs in any age group with mean age of 49.5 years and equal sex incidence[10].
One third to half are asymptomatic mass, one third presents with symptoms like cough, dyspnoea, chest pain, dysphagia, hoarseness and recurrent infection and the remaining one third presents with paraneoplastic syndrome.

Classification of Thymic Epithelial Neoplasm:
The classification has been confusing and controversial for many years[1]. The various classification included Muller-Hermelink and Suster-Moran classifications. Due to its difficulty in reproducibility ,WHO suggested a modified classification in 2004 which reflects invasiveness and immunological function of thymic epithelial tumors[1].
WHO listing includes Epithelial tumors ,Germ cell tumors, Neuroendocrine tumors, Lymphoma, Mesenchymal, Ectopic tumors, Tumor like lesions, Metastatic tumor and Unclassified [2] tumors. The frequency of occurrence according toWHO classification in Type A is 4-19%; Spindle cell type, Medullary, in Type AB is15-43%; Mixed Type, in Type B1 is 6-17%;Lymphocyte rich,lymphocyte predominantly cortical, in Type B2 is 18-42%;Cortical, in Type B3 is 7-25%; Atypical, Squamoid, Well differentiated Thymic carcinoma[13], in Type C is less than 10% ; keratinising and non-keratinising squamous cell carcinoma, muco-epidermoid, basaloid, lympho-epithelioma-like,small cell/ neuroendocrine, sarcomatoid, clear cell and undifferentiated/ anaplastic[18]

Thymoma: Incidence 1-5 per million/ year [13]
Macroscopy:
Tumors vary in size from microscopic to large which are round to oval and are covered by fibrous capsule of variable thickness. The cut surface show tan coloured fleshy lobules delineated by fibrous septa. Cysts, foci of haemorrhage and calcification are common. Invasive types show breached capsule.
Microscopy:
Tumor composed of lobules separated by thin and thick acellular fibrous bands which show focal calcification. The epithelial cells are large and appear syncytial, ovoid or polygonal and are pale stained with regular, round vesicular nuclei. These cells are arranged in sheets, clusters, pseudo-rossette, anastomising networks, ribbons etc. Variably lined perivascular spaces are broadened by neoplastic epithelial cell which are filled by proteinaceous material.

Type A is composed of neoplastic spindle -shaped epithelial cells without atypia or lymphocytes; showing bland nuclei, dispersed chromatin and inconspicuous nucleoli.
Type B1 shows epithelial cells scattered in a prominent population of immature lymphocyteswith pale areas of medullary differentiation, with or without Hassal's corpuscles.
Type B2 thymoma is composed of large, polygonal neoplastic cells arranged in a loose network with their large nuclei displaying an open chromatin pattern with prominent central nucleoli.

Type B3 is composed of medium-sized round or polygonal cells with slight atypia with a very minor component of intra-epithelial lymphocytes, resulting in a sheet-like growth pattern and tumor cells-form lobules that are separated by thick fibrous and hyalinised septa and have round or elongated,folded or grooved nuclei with less prominent nucleoli .

Immunohistochemistry:

The neoplastic epithelial cells are positive for Cytokeratin, EMA, p63, PAX8, CD20 and are negative for CD5, CD117 which differentiates from Type C Thymoma which is positive for CD5 and CD117. The immature T lymphocytes exhibit cortical thymocyte phenotype of TdT, CD1a, CD99a positive. [10].

Electron microscopy:

The neoplastic epithelial cell shows multiple interdigitating elongated cell process connected by desmosome and intercytoplasmic tonofilaments are prominent.

Cytogenetics:

Type B3 thymoma show deletion of chromosome 6 and 13q, with a gain of 1q, Type A shows loss of 6p[13]. Prognostic factors:

Prognostic factors:

Tumour stage is the most significant prognostic factor[3,10,12,13].

Completeness of excision.

Histologic type

Tumor size

Performance status Differential diagnosis[10,13].

Carcinoid tumor- 2-5% of Thymic Epithelial Tumors
Hodgkin lymphoma
Lymphoblastic lymphoma- 2-3% of NHL
Thymic carcinoma (Type- C, WHO classification)
Mesenchymal tumours for Type A Thymoma
Germ cell tumor- less than 1% of all neoplasms

CASE REPORT:

A 45 year old male presented with features of difficulty in breathing, cough with expectoration for the past 7months.

Investigation:

X-ray chest:lobulated shadow with calcification in anterior superior mediastinum (FIG-1) S/O: Anterior mediastinal mass. CT-chest: 12.4x8.8cm, well defined heterogeneous soft tissue mass lesion in left paratracheal regionand anterior mediastinum displacing the trachea.(FIG-2, 3) MRI-Brain:T2 hyperintense signal in Temporal lobe

Cytology:
Guided FNAC – The smear studie showed distinct population of cohesive epithelial cells admixed with few lymphocytes(FIG-3) The cells were large round to oval with increased nuclear cytoplasmic ratio and pale eosinophilic cytoplasm. (FIG-4)

Per operative finding:
Mass was identified lying in the anterior mediastinum as a firm to hard with infiltration into left lung upper lobe ,underlying mediastinal structures and anterior chest wall. Further dissection was not possible as it was widely invasive.
Clinical stage (Masaoka-Koya) was stage-III. TNM staging (Yamakawa et al) was T3N0M1. Tissue biopsy was sent for Histopathological examination

Histopathological finding:
Macroscopy:
Received three soft tissue fragments with largest measuring 2x1x1cm and smallest 1x1x1cm.

Cut surface:
Greyish yellow with intervening brownish areas and was firm in consistency.

Microscopy:
H&E: The tumor was composed of syncytial population of neoplastic epithelial cells which were spindle shaped .Few non neoplastic lymphocytes were also seen. (FIG-6, 7)The tumor cells were arranged in lobules with round to polygonal shape with mild atypia, round to oval vesicular nuclei and small nucleoli. (FIG-8) Few areas showed squamoid differentiation with oval to irregular nuclei and eosinophilic cytoplasm (FIG-9). Vascular emboli was present (FIG -10).

Immunohistochemistry:
Cytokeratin, the marker for epithelial cell was done. The epithelial cells were ovoid to polygonal evenly spaced with cytoplasmic membrane positivity and few delicate cytoplasmic processes were seen.(FIG-11,12)

Diagnosis as per WHO classification:
MALIGNANT THYMOMA- TypeB3 and Type A.

DISCUSSION: Thymoma is restricted to neoplasms of thymic epithelial cells, independent of the presence or number of lymphocytes[9]. Suster and Moran et al showed that numerous reports have emphasized the difficulty of establishing clinicopathologic correlation in thymoma, due to wide histologic appearances[1,2,3,4,5].

The predominant histological subtypes in most published series are TypeB2 and TypeAB [20-35%] each.TypeB1 and TypeA [5-10%] each. Mean age for TypeB3 is 45-50 years and incidence is 7-25% of all Thymomas in a study by William D.Travis et al[13] .

The diagnosis of our case with respect to Muller –Hermelink classification is Well differentiated Thymic Carcinoma, Suster – Moran classification is Atypical Thymoma and as per Proposed Suster – Moran classification is Moderately Differentiated Thymic Carcinoma.[1] These terminologies may be confusing for the clinician to treat the patient. More over histological appearance varies greatly from tumor to tumor. The neoplastic epithelial cells have morphological variability in shape from spindle to polygonal and atypia. Nearly all thymomas are of malignant potential and are invasive. Close relationship exists between microscopic subtype and likelihood of invasion;

Type A<AB<B1<B2<B3<C [9]. Pescarnoma et al has claimed that the two most important prognostic determinants were gross findings at surgery and the association with myasthenia gravis [3]. John K.C.Chan et al showed macroscopically the prognosis is excellent for encapsulated tumors and the locally invasive thymomas have less favourable outcome. But the recent trend is to accord histological features, an increasingly more important role in prognosis. Tumor size greater than 11cm is an unfavourable prognositic factor[10].hence multifactorial factors like; Histology, Staging, Status of Resectability, Tumor size decides the prognosis as suggested by Meinoshin Okimura et al[14]

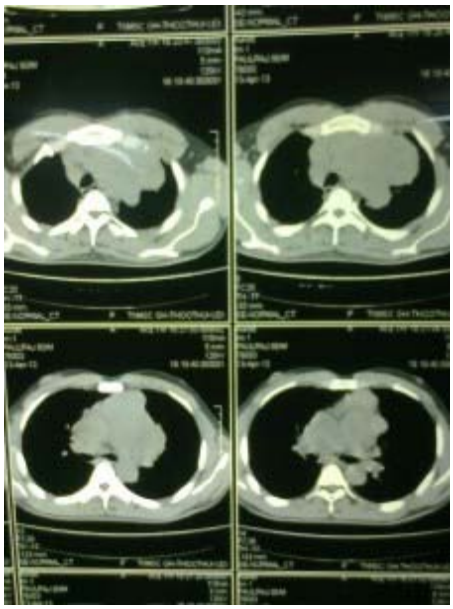


FIGURE-2, CT SCAN, CHEST, Shows well defined heterogenous soft tissue mass lesion in left paratracheal and anterior mediastinum

CONCLUSION

Though primary tumors of Thymus are uncommon, Thymoma is the commonest primary tumour of Thymus. Multiple factors determine the prognosis namely WHO Histological Type, Clinical

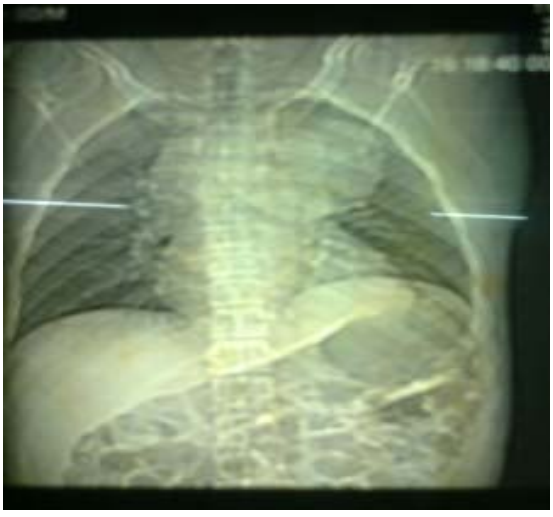


FIGURE-1, CHEST X-RAY,Showing lobulated shadow with calcification in Anterior superior mediastinum

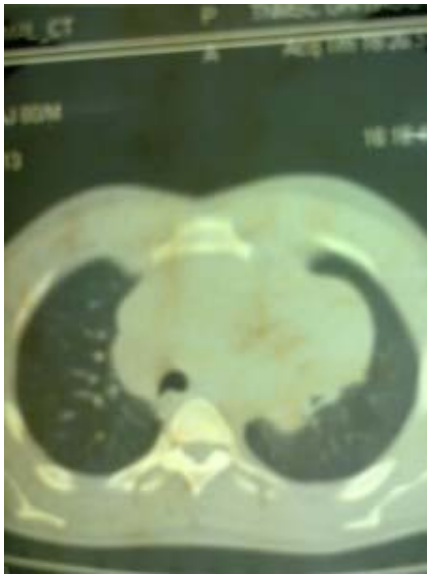


FIGURE-3, CT-SCAN,CHEST, Showing heterogenous soft tissue mass lesion involving anterior chest wall

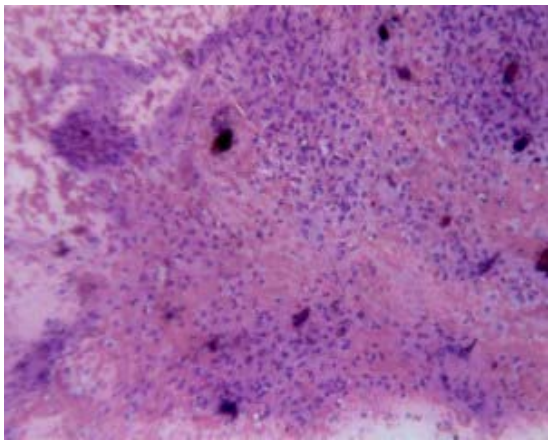


FIGURE-4, CYTOLOGY- H&E-100X Showing cohesive epithelial cells admixed with few lymphocytes

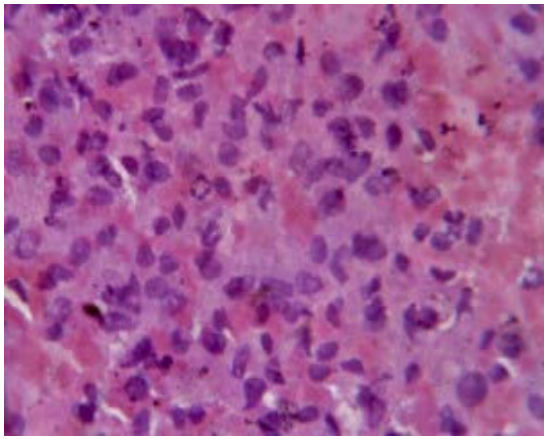


FIGURE-5,CYTOLOGY- H&E-400X, Shows large round to oval epithelial cells with increased nuclear cytoplasmic ratio and pale eosinophilic cyto-

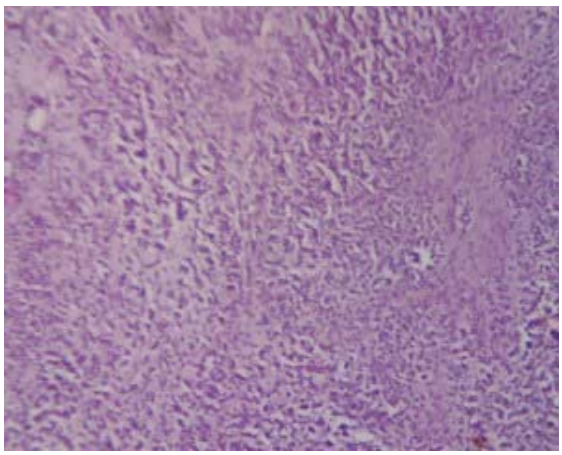
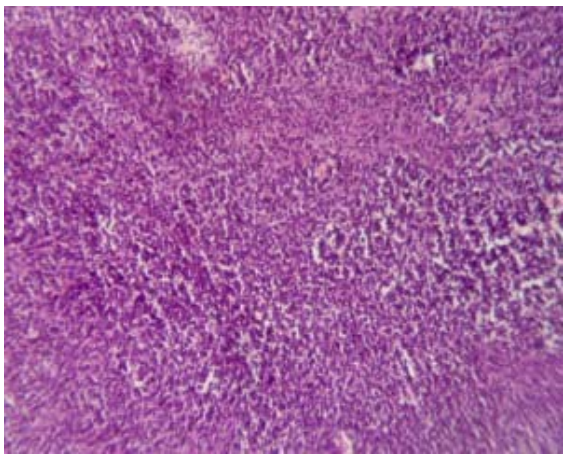


FIGURE-6, H&E- 100X, Shows syncytial population of neoplastic epithelial cells
FIGURE-7, H&E,100X, Showing neoplastic epithelial cells with few lymphocytes



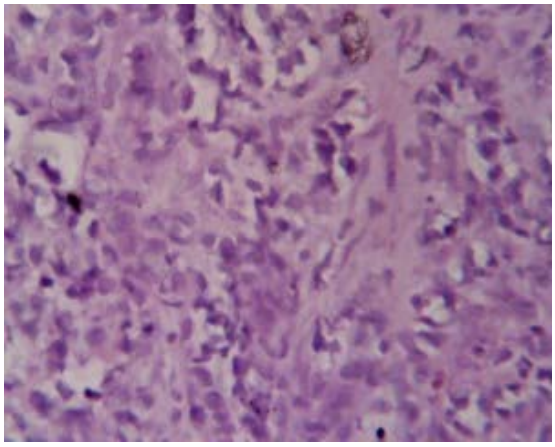


FIGURE-8,H&E,400X, Showing cells arranged in lobules with mild atypia, round to oval vesicular nuclei, small nucleoli and few spindle cells.

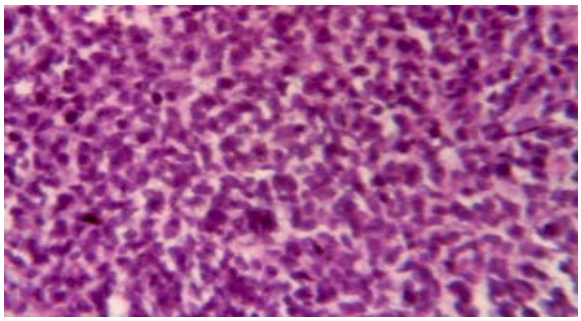


FIGURE-9,H&E,400X, Showing squamoid differentiation with oval to irregular hyperchromatic nuclei and scanty eosinophilic cytoplasm

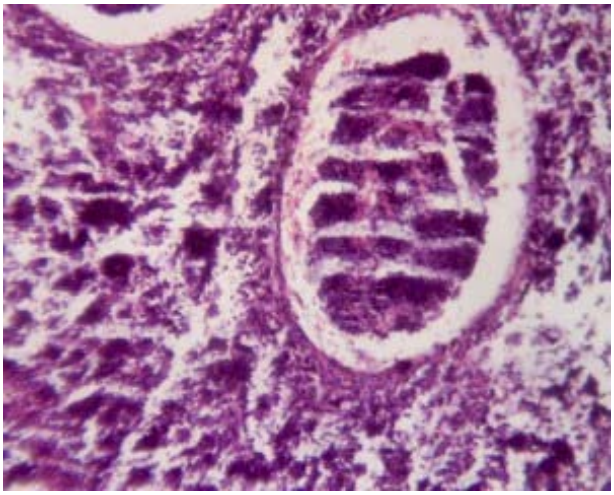
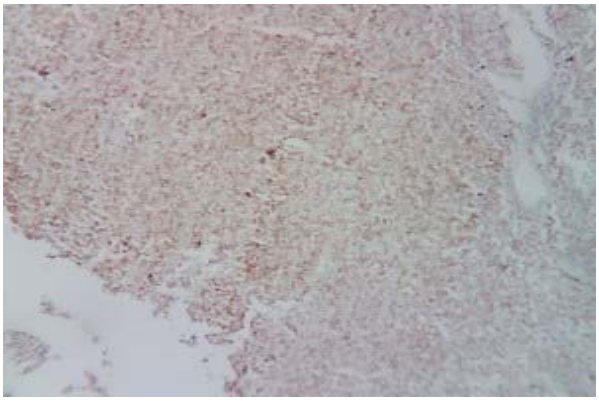


FIGURE-10, H&E,100X, Showing Vascular emboli FIGURE-11, IHC, CYTOKERATIN, 100X, Showing diffuse cytoplasmic positivity



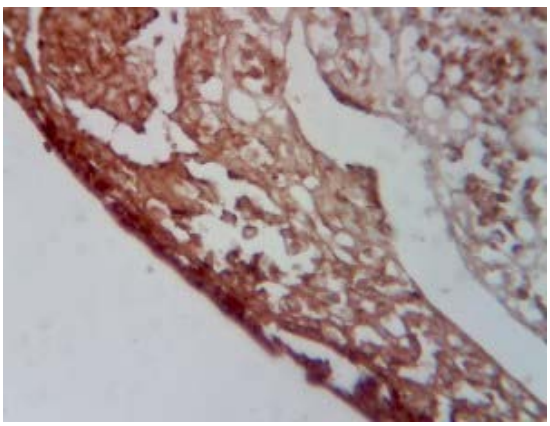


FIGURE-12,CYTOKERATIN,400X, Showing ovoid to polygoanal cells with diffuse cytoplasmic membrane positivity.

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