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Primary thymic carcinoma

An unusual case originating in a lymphocytic rich thymoma *

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Summary. A case of thymic carcinoma arising within a lymphocyte rich thymoma is reported. The undifferentiated carcinoma contained cellular elements resembling choriocarcinoma but could be differentiated therefrom by positive staining for prekeratin antigen and an absence of staining for B-HCG antigen utilizing immunohistochemical techniques.

Key words: Thymoma – Thymic carcinoma – Ultrastructure – Immunohistochemistry

Introduction

Histologically, thymomas are classified into lymphocyte-rich, epithelial, mixed and spindle cell types [1, 2, 6]. Their behavior is determined by the presence or absence of extension into surrounding mediastinal or thoracic structures. In addition, a cytologically malignant form of thymoma, thymic carcinoma, has been documented. We report the occurrence of a thymic carcinoma arising within a lymphocytic-rich thymoma and mimicking a choriocarcinoma. To the best of our knowledge, no identical case has been reported previously. Wick et al. [9] documented a case of a sarcomatoid thymic carcinoma complicating an epithelial-rich thymoma as well as a neuroendocrine-type thymic carcinoma developing from a thymic carcinoid tumour.

Materials and methods

Tissue for electron microscopic and immunoperoxidase studies was retrieved from formalin. Immunohistochemistry for prekeratins, B-HCG, α-antitrypsin and alphafetoprotein were performed utilizing the PAP method described by Sternberger [7]. The sections were deparaffinized through xylene and alcohol to water and endogenous peroxidase blocked with 0.3% H_2O_2

* Dedicated to Professor Karl Lennert, Kiel, on the occasion of his 65th birthday

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Table 1. Classification of malignant thymomas

I.	With no or minimal cytological atypia
	a Locally invasive (usual form)
	b With true lymphatic or haematogenous spread (rare)
II.	Cytologically malignant (=thymic carcinoma) morphological variants
	a Squamous cell carcinoma
	b Lymphoepithelioma-like
	c Clear cell carcinoma
	d Sarcomatoid (electron microscopy often needed to distinguish from epithelial tumours)
	e Undifferentiated (electron microscopy often needed to distinguish from histiocytic lymphoma and germ cell tumours)

in menthanol. Nonspecific staining was blocked by applying normal swine serum 1:10 for 20 min. The sections were incubated with primary antibody (rabbit anti-human) for 20 min, washed with phosphate buffered saline (PBS) and then incubated with the secondary antibody (swine anti-rabbit globulin) 1:20 for 20 min, followed by a second PBS wash. Following incubation with PAP 1:50 for 20 min and a PBS wash, the sections were incubated with AEC substrate (0.02% 3 amino-9 ethyl carbazole, 0.03% H_2O_2, 5% NN dimethyl formamide in 0.1 M acetate buffer pH 5.2). Tissue was prepared for electron microscopy by standard techniques.

Case history

A 35-year-old asymptomatic Israeli-born female was found to have a large anterior mediastinal mass on routine chest roentgenogram. The x-ray and a CT-scan showed a 10×6 cm mass with central necrosis infiltrating the middle lobe of the right lung. A bone scan and routine laboratory investigations were within normal limits. A right-sided thoracotomy was performed and a tumour was resected from the anterior superior mediastinum together with the right middle lobe of the lung. On the basis of an initial histological suspicion of choriocarcinoma, a serum HCG was performed 2 week post-surgery and was found to be negative. The post-operative course was uneventful and the patient was given Bleomycin, Velbe and Cisplatinum. The tumour recurred within 2 months and the patient died 5 months post-surgery. Permission for autopsy was not obtained.

Pathologic findings

Macroscopic features. A multilobular mass measuring $15 \times 10 \times 8$ cm was firmly adherent to the lung lobe. The cut surface was tan-colored and coarsely lobulated with large areas of necrosis (Fig. 1). Some of the nodules had a more cream-colored, 'fish-flesh' appearance.

Microscopic features. The histological sections showed two distinctly different patterns in intimate contact with one another. Sections taken from the nodules with the 'fish-flesh' appearance showed features of a typical lymphocytic-predominant thymoma (Fig. 2). Sparse epithelial thymocytes were

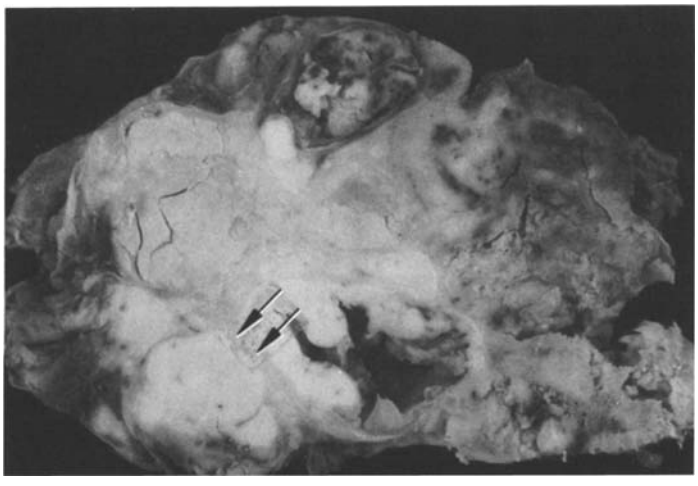

Fig. 1. Cut surface of mass showing paler nodule corresponding to thymoma (*arrow*) surrounded by thymic carcinoma

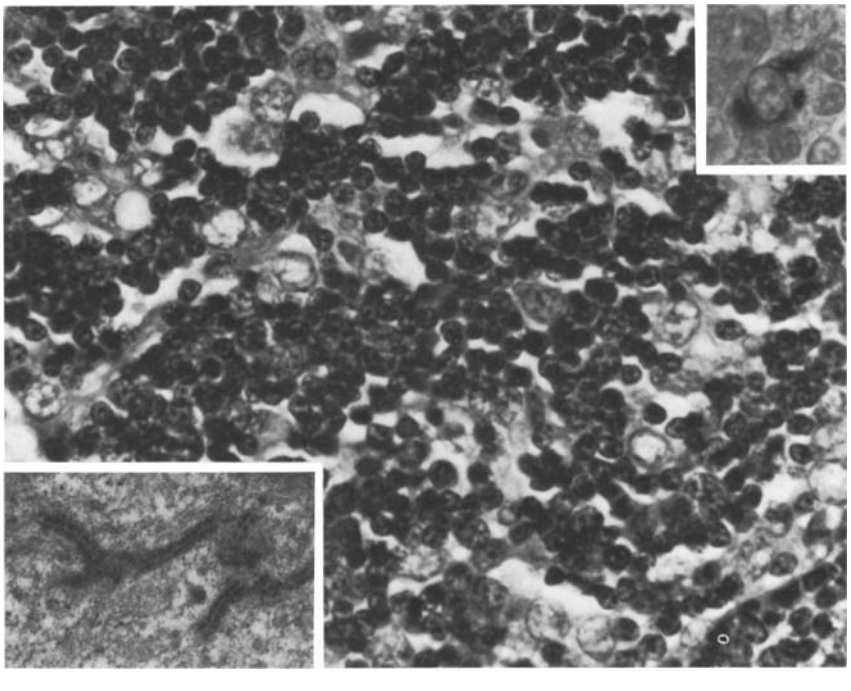

Fig. 2. Thymoma composed of scattered epithelial thymocytes and normal-looking lymphocytes (×600). *Inset upper right* – shows positive prekeratin staining in thymocyte (PAP ×900). *Inset lower left* – electron micrograph showing wellformed desmosomes of thymocytes (×25,000)

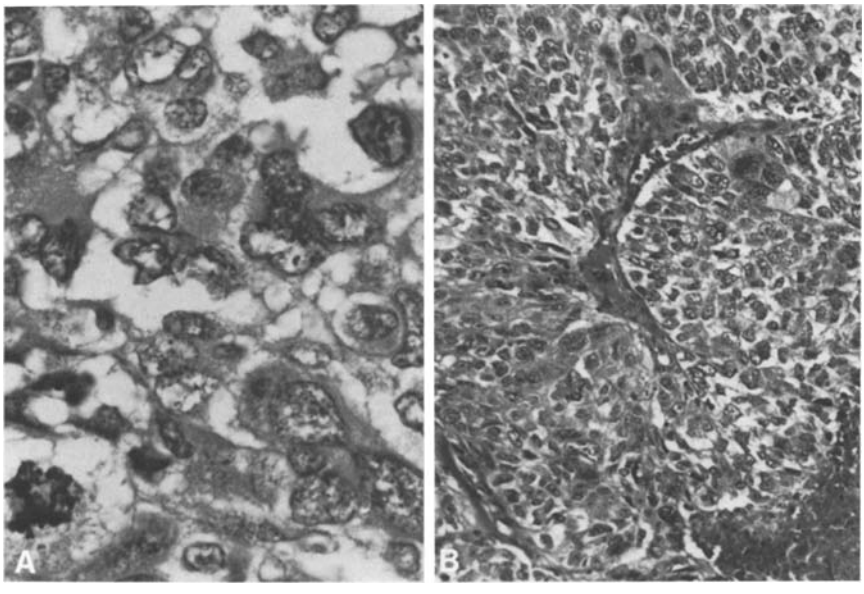

Fig. 3A, B. Sheets of carcinoma cells including multinucleate forms and abnormal mitotic figure (**A** = ×112; **B** = ×450)

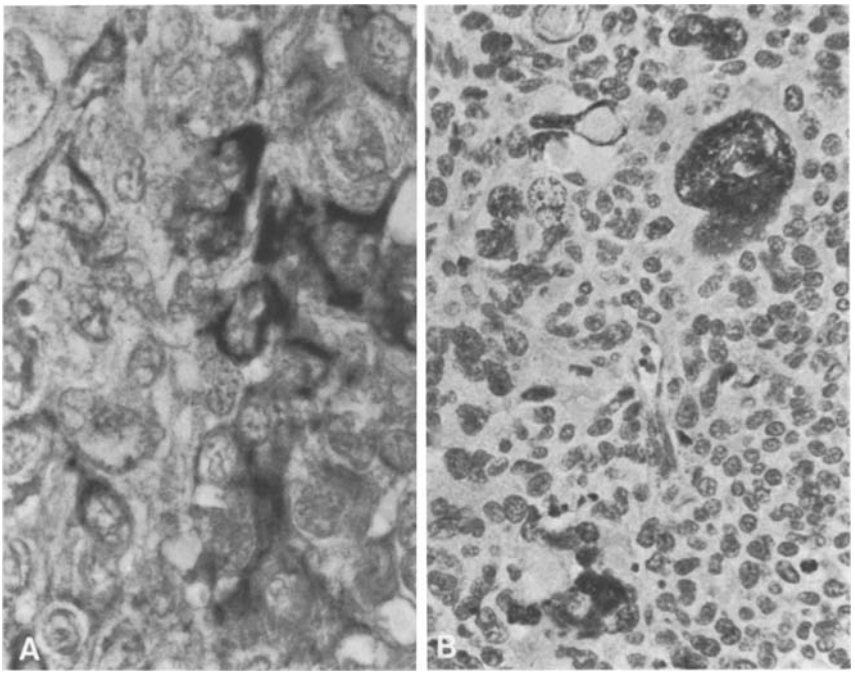

Fig. 4. A Numerous prekeratin positive cells in thymic carcinoma (PAP ×450). **B** Negative staining of giant cells in thymic carcinoma for B-HCG (PAP ×450)

scattered singly or in small clusters of 2–3 cells amidst a sea of mature-looking lymphocytes. A few mitotic figures were present within the sheets of lymphocytes. The second component of the lesion consisted of sheets and nests of large, highly atypical polygonal cells with abundant eosinophilic and clear cytoplasm, large and atypical nuclei and many mitotic figures, including abnormal forms (Fig. 3A, B). In addition to sheets of uninucleate cells, scattered bizarre multinucleate cells resembled syncytiotrophoblast. Tumour invasion of blood vessels was present.

Electron microscopic features. Although cell preservation was poor because of prior fixation in formalin, the salient ultrastructural features were still recognizable. The scattered thymocytes had regular, ovoid nuclei with a prominent euchromatin pattern. These cells possessed elongated dendritic processes with desmosomal attachment sites (Fig. 2, inset). They were interspersed amongst small lymphocytic type cells. The sheets of large, anaplastic cells had large, irregularly shaped nuclei and numerous well-developed desmosomes. Some long-spaced collagen was present within the intercellular matrix.

Immunohistochemical features. The lymphocytic sheets stained negatively with all the immunoglobulin antisera. A few scattered macrophages and neutrophils stained positively for lysozyme. The scattered epithelial thymocytes stained positively for prekeratin (Fig. 2, inset). The sheets of undifferentiated polygonal cells showed intense staining in the majority of cells, including the multinucleate forms with the prekeratin antibody (Fig. 4A). Stains for HCG (Fig. 4B), alpha-1-antitrypsin and alphafetoprotein were uniformly negative.

Discussion

The light microscopic, ultrastructural and immunohistochemical features of the present tumour indicate the occurrence of an undifferentiated carcinoma developing within a lymphocytic-rich lymphoma. All thymomas are neoplasms of thymic epithelial origin with a variable component of the neoplastic epithelial cells in the several histological subtypes. The thymic epithelial cells are cytologically bland with few or absent mitotic figures and successful resection is usually associated with cure. Recurrent and aggressive behaviour is observed when the tumour grossly infiltrates adjacent structures [4]. In addition to these usual histological variants of thymoma, a thymic carcinoma composed of sheets of cytologically malignant epithelial cells has been described and is invariably associated with an aggressive course [3]. Wick et al. [9] described 20 primary thymic carcinomas from the files of the Mayo Clinic. Thirteen of their cases were poorly differentiated and the cells resembled those of a lymphoepithelioma while four had the histological characteristics of a small cell neuroendocrine carcinoma. In the remaining three tumours, the epithelial cells were spindled or sarcomatoid. Thomson and

Thackray [8] reported 20 'undifferentiated' neoplasms amongst their series of 54 thymomas. The true incidence of thymic carcinoma is unclear since most series fail to categorize such cases specifically or deliberately exclude them. A review article dealing with thymic hyperplasia and neoplasia by Levine and Rosai [3] offers a most useful classification of malignant thymomas (see Table).

The presence of a thymic carcinoma arising in association with a lymphocytic-rich thymoma as in our case is unusual. We speculate that the thymoma had been present for a prolonged period and that the rapid progression of the lesion was determined by the superimposed thymic carcinoma. One of the 20 thymic carcinomas described by Wick et al. [9] was noted to be associated with a thymoma. In that case, the thymoma was composed of numerous bland epithelial cells with scanty admixed lymphocytes. The carcinoma was composed of sarcomatoid-looking cells which traversed the thymoma as narrow fascicles. A second thymic carcinoma of neuroendocrine type had developed in association with a thymic carcinoid tumour.

The differential diagnosis in the present case would include a thymoma associated with mediastinal histiocytic lymphoma, a choriocarcinoma or a metastatic carcinoma. Histiocytic lymphoma of the mediastinum is also composed of sheets of large atypical cells with abundant pale cytoplasm [5]. Fibrous bands tend to segregate nests of cells and so heighten a resemblance to a malignant epithelial tumour. The large, vesicular nuclei are frequently notched or grooved. An immunological study of 19 such lesions by Yousem et al. [10] demonstrated B cell features in 18 and T-helper cell features in one. A teratoma of the anterior mediastinum including choriocarcinomatous elements is composed of large uni- and multi- nucleate cells closely resembling the undifferentiated element of the present tumour but which can be readily distinguished using immunohistological techniques. The presence of a metastatic carcinoma within a thymoma would be distinctly unusual and a thorough work-up in this patient failed to reveal any primary pulmonary or other primary tumour.

The recognition of a thymic carcinoma is important because its behaviour is considerably more aggressive than thymoma. Only one of the 20 cases of thymic carcinoma in the series of Wick et al. [9] was free of disease four years following therapy and another was alive but with metastatic and residual mediastinal tumour; the remaining patients had all died with an average survival of 18 months following diagnosis. This is in sharp contrast to the longer survival times in patients with ordinary thymomas.

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