Thymoma: A pathological study of 50 cases

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Received : 16-02-04
Review completed : 23-03-04
Accepted : 11-05-04
PubMed ID :
J Postgrad Med 2004;50:94-7

ABSTRACT

Background: A combination of epithelial cells and lymphocytes results in a varied histomorphology of thymomas and consequent varied classification systems.

Aim: To correlate the Marino and Muller-Hermelink (MMH) classification with the invasive behaviour of thymomas.

Setting and Design: Retrospective analysis.

Materials and Method: Thymomas encountered in the past 21 years were re-classified with the MMH classification and correlated with Masaoka's staging and clinical presentation.

Results: The thymomas formed 91% of the primary thymic epithelial tumours. Predominantly cortical thymomas (n=21) and cortical thymomas (n=22) were the common subtypes and 60% and 77% of these, respectively, were in stages II or III. Cystic change, necrosis or haemorrhage played no role in predicting invasive behaviour. Cortical epithelium correlated well with the presence of para-thymic syndromes, especially myasthenia gravis.

Conclusion: MMH classification is easy to apply. Cortical thymomas in stage I should be followed up for possible recurrence.

KEY WORDS: Thymoma, Marino Muller-Hermelink classification, Masaoka's staging

Besides playing a crucial role in the differentiation of T lymphocytes, the thymus is a site for a spectrum of tumours and tumour-like lesions. Among the tumours, thymomas form an important group. They pose a diagnostic challenge to the pathologists by their array of histological features resulting in varied methods of classification. In this study, we have employed the Marino and Muller-Hermelink classification (MMH)[1,2] for categorizing the thymomas and have correlated it with the staging system of Masaoka et al.[3]

Materials and Method

This is a retrospective study, conducted at a large teaching hospital. All thymomas, biopsied or surgically excised over a period of 21 years (1983-2003) were studied. Autopsies performed in the same period were also analysed. All slides (six to 12 per case) were reviewed. The thymomas were reclassified as per the MMH classification into five subtypes: medullary (MT), mixed (MiT), predominantly cortical (PCT), cortical (CT) thymomas and well-differentiated thymic carcinomas (WDTC).[1,2]

Carcinoids and carcinomas (bearing resemblance to their counterparts at other sites) were excluded. The clinical details noted were age and gender of the patients, presentation and operative notes/investigations with special reference to the anatomical location and surgical margins. On gross examination, emphasis was laid on the presence of the capsule, its invasion and the presence and degree of necrosis, haemorrhage and cystic degeneration. Other features noted on microscopy were the presence of perivascular spaces, medullary differentiation, Hassal's corpuscles and more importantly, capsular micro-invasion. The histological diagnosis was then correlated with Masaoka staging.[3]

Results

Among a total of 55 primary thymic epithelial tumours, there were 50 thymomas (91%). All were located in the anterior mediastinum. Forty-three thymomas were surgically excised. Five were detected at autopsy, while two were diagnosed by guided percutaneous mass biopsies. There were 33 males and 17 females, including two children (9-year-old male and 11-year-old female). The oldest patient was 63 years old. The tumour occurred in an almost equal proportion in the third and fifth decades of life. Many of the tumours were large (more than 8 cm) and all had the characteristic lobulated, homogeneous grey-white cut surface.

The histological characterisation of the tumours and their stages are tabulated in Table 1. Twenty-one tumours (42%) fell into the category of **predominantly cortical thymomas** (PCT). The tumours ranged in size from 4x 2.5 x 1 cm to 18 x

Table 1: Type and staging of thymomas (N=50)

Histology	Stage I	Stage II	Stage III
Predominantly cortical (n=21)*	08	09	03
Cortical (n=22)	05	13	04
Medullary (n=04)*	03	-	01
Mixed (n=03)	02	01	-

*One case diagnosed on biopsy, no case of stage IV were seen

12 x 8 cm. Eighteen were wholly or partly encapsulated, while the remaining three had infiltrative margins. All the tumours had lymphocyte-rich lobules, separated by thin fibro-vascular septa. The epithelial cells were barely discernible, polygonal in shape with a moderate amount of pink cytoplasm, round to ovoid vesicular nuclei and small nucleoli (Figure 1a). One of them was diagnosed on biopsy. Of the remaining 20 cases, 12 tumours (60%) were in stages II or III. **Cortical thymomas** (CT) formed the second group with 22 tumours (44%). The sizes ranged from 2 cm to 15 x 13 x 6 cm. Incidentally, one patient, an 18-year-old male, had two well encapsulated tumours. These tumours too retained a lobular architecture with sheets or islands of epithelial cells and a sprinkling of lymphocytes. The cells were large with abundant eosinophilic cytoplasm, large vesicular nuclei and prominent nucleoli (Figure 1b). None showed mitosis or pleomorphism. Seventeen tumours (77%) were in stages II or III and the others in stage I. There were four (8%) **medullary thymomas** (MT). These were characterized by a monotonous population of innocuous spindle-shaped cells with fascicular pattern (Figure 1d). The cytoplasm was moderate to scanty. The nuclei were ovoid with inconspicuous nucleoli. Scattered small lymphocytes were seen in the background. Three were small and encapsulated while one was diagnosed on biopsy in a 57-year-old male with an infiltrative mediastinal mass. Three tumours (6%) had an admixture of two components, spindle-shaped epithelial cell areas resembling MT and areas similar to PCT and were designated as **mixed thymomas** (MiT, Figure 1c). One was seen incidentally at autopsy. All were encapsulated, with capsular micro-invasion in one. One tumour was only 0.6 cm in diameter (microscopic thymoma).

Peri-vascular spaces, abortive Hassal's corpuscles and medullary differentiation were common in PCT and its counterpart MiT (43.5%), as compared to CT. None of the above features were seen in MT. Cystic degeneration, necrosis, fresh and organized haemorrhage were largely seen in PCT and CT, irrespective of their sizes. Extensive cystic change in PCT (Figure 2), lead to clinical diagnosis of mediastinal cyst. Coagulative necrosis in one of the thymomas, was due to arterial intimal

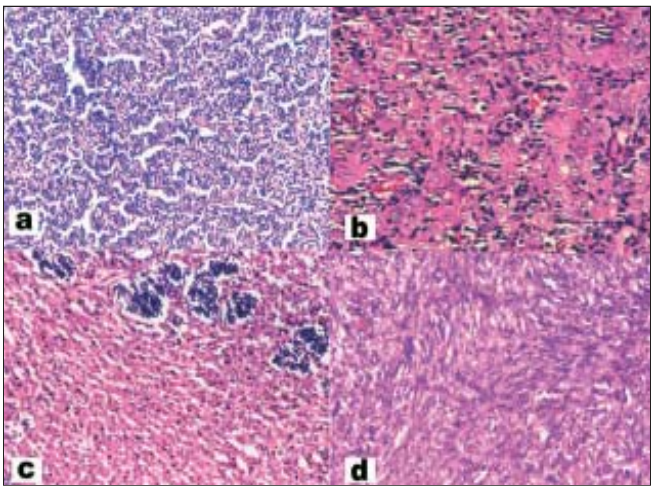

Figure 1: Thymoma, typical morphology of a) Predominantly cortical, b) Cortical, c) Mixed and d) Medullary types (H&E x 250)

Figure 2: Extensive cystic change in thymoma with a clinical diagnosis of mediastinal cyst

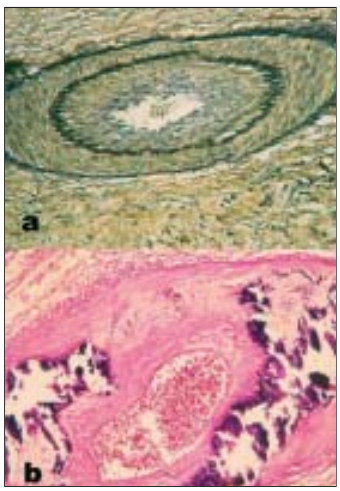

Figure 3: Vascular changes a) Intimal fibroplasia (EVG x 250), b) Monckeberg's sclerosis-like change (H&E x 250)

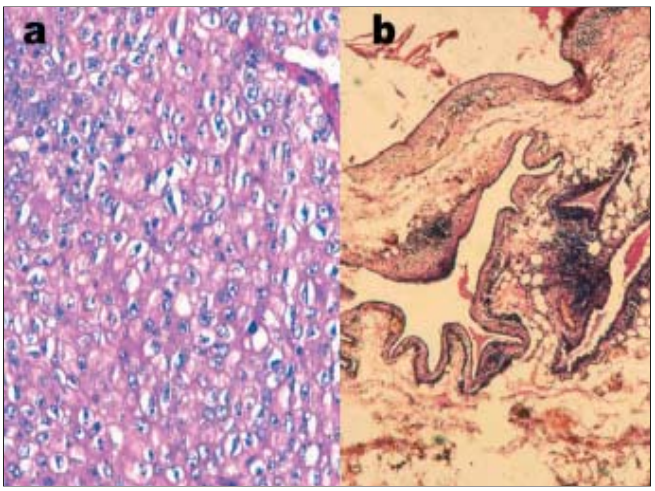

Figure 4: Cortical thymoma with a) Squamous differentiation (H&E x 250), b) Multilocular cyst-like area (H&E x 19)

fibroplasia-like changes (Figure 3a). The same case also had venular thrombotic changes. Other vascular changes seen were Monckeberg's sclerosis (Figure 3b) and tumour embolisation, in two cases each. Calcification, sometimes of the psammomatous type, was seen in seven cases. Squamous differentiation (Figure 4a) was present in two, with formation of keratinous cysts within. One among them also revealed multi-locular cyst-like areas (Figure 4b) outside the tumour. CT areas and PCT areas were seen in one and two cases of PCT and CT respectively. Additionally, follicular hyperplasia was seen in the surrounding atrophic thymuses in three.

All patients were symptomatic, save one who had an incidental thymoma at autopsy. Thirty-eight patients presented with para-thymic syndromes. Thirty-six had myasthenia gravis (two months to six years duration), of these 14 cases were PCT, 18 CT and two cases each of MT and MiT. Pure red cell aplasia and polymyositis were seen in a case each of PCT and MT. The remaining 11 had symptoms related to compression such as cough, chest pain, dyspnoea, dysphagia, and superior vena caval syndrome.

Discussion

Thymoma is the most common primary tumour of the anterior mediastinum, forming 15% of all mediastinal tumours, especially in adults over 40 years of age.[4,5] We found that they constituted 32% of all tumours and tumour-like lesions of the thymus. Seventy per cent of the thymomas in this series were seen above 40 years of age and predominantly in males. They are rare in children.[6] In the present series, there were two children (4%).

Several systems of classification of thymomas have made their appearance with clockwork regularity over the years. All our cases retrieved over 20 years were initially classified according to the Bernatz-Lattes[7,8] or Rosai-Levine classifications.[9] and were now classified by the MMH system.[1,2] Many studies have been conducted to evaluate the MMH classification.[10-15] The authors found that the histological types as classified by the MMH system correlated well with invasive growth. However, other studies have produced conflicting results regarding the reproducibility of the classification, which they felt as being 'conceptually attractive'.[16-18] They preferred surgical staging for prognosis. Kuo's and the WHO classifications[19,20] appear to be variations of the MMH classification. We too found the application of the MMH classification preferable, as it is more descriptive when compared to the other recent classifications. The Indian study by Sundaram et al[15] had a high incidence of MT (26.6%) as compared to other studies, including ours (5 to 12%).

Complete surgical resection is the mainstay of the treatment with adjuvant radiotherapy or chemotherapy in the higher stages.[21-23] Despite complete resection, recurrence is an anticipated problem, varying from 11 to 36% in invasive thymomas and up to 10% even in the encapsulated thymomas, occurring months or years following excision.[4,5,22] Thus, it would be better to consider staging as well as histopathological classification as independent prognostic factors.[24-26] We too, are of a similar opinion. This is especially true if thymomas of 'high grade' histomorphology i.e. the CT type are found to be in stage I. Hence, follow-up for recurrence is advisable in such cases. It is thus possible that recurrences in the clinical series of encapsulated tumours had a high grade histomorphology, though pathological data is lacking.[4,5,22]

Close et al[13] found discrepancy in classifying 22 % of their tumours. They recommend an adequate number of sections. In our series, cortical thymoma-areas in predominantly cortical thymomas and vice versa were found in one and two cases respectively. Similarly, areas of squamous differentiation were found in two cortical thymomas. We followed the recommendation that if more than 75% of the tumour shows a particular pattern, then it should be assigned to that category.[13] The authors[13] also caution against diagnosis on biopsies, as also highlighted in our study.

There is a considerable variation in the size of the thymomas. Twenty-six of our tumours were more than 5 cm in size, which is associated with a higher rate of recurrence.[21] Sometimes, the tumour can be microscopic,[27] as seen in one of our cases. Hence, it is advisable to take multiple sections in grossly 'non-neoplastic' thymectomies for myasthenia gravis. Additional gross features are cystic degeneration, necrosis and haemorrhage. Cystic change can be so extensive as to simulate thymic cyst,[28] seen in one case. Apart from distension of the peri-vascular spaces, cystic areas can also occur due to necrosis, cystic squamous differentiation or multi-locular cyst-like areas,[29] as seen in a few of our cases. We also found haemorrhage and necrosis in four thymomas due to vascular changes[30] ('tumour-induced vasculopathy'). These changes can often be missed because there is a tendency to avoid sampling of obviously cystic or necrotic areas. The changes, thus, play no role in the prediction of clinical behaviour. But sampling is advocated to not only demonstrate vascular lesions, but also to detect lurking foci of thymic carcinoma.[31] We did not find such carcinomatous foci in any of our tumours.

Reports in the literature indicate that 30 to 50 % of thymomas are asymptomatic. [4] All our patients were symptomatic, save one, which was discovered only at autopsy. Twenty two per cent presented with local pressure symptoms, while the remaining had para-neoplastic syndromes, especially myasthenia gravis present in 72 % of cases, well within the reported range.[4]

The MMH classification is at present the better classification and can indicate the behaviour of a given tumour. Given the variable histological pattern, biopsies (particularly CT-guided) may prove misleading in identifying the exact histological type.

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