

Thymic Diseases as Revealed by a Series of Consecutive Thymectomies and Biopsies from the Thymus

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ABSTRACT

A series of 85 thymic biopsies and specimens from thymectomies were re-examined. Forty-five of these were taken from patients with myasthenia gravis. A relatively low frequency of thymitis (57%) was found in these patients, while the frequency of thymoma (9%) was as expected. Two cases of thymitis in thyrotoxicosis were included in the material. In all, 22 thymomas of various kinds (18% of the total material) were diagnosed. A fairly low proportion of these thymomas (18%) were from patients with myasthenia gravis.

INTRODUCTION

Our increasing knowledge about the functions of the thymus and the fact that some pathological conditions of this gland seem to be associated with several other diseases justifies a systematic investigation of thymic disorders. In the present investigation specimens from a 12-year series of consecutive thymectomies and thymic biopsies were re-examined in order, among other things, to gain further knowledge about the relative distribution of thymic diseases in such materials. Further, the terminology of thymic diseases is somewhat confused and another purpose of the investigation was therefore also to contribute towards a uniform histo-pathological terminology.

MATERIAL AND METHODS

During the years 1961–1972, 85 specimens taken from thymectomies and thymic biopsies were examined in routine diagnostic work at the department (total number of surgical specimens during this period 210720). In 66 cases, total thymectomy was performed. In 19 cases a biopsy from the thymus was taken. The histological staining techniques used were van Gieson (v. G.) and haematoxylin-eosin (H.-E.). After examination of the specimens, they were classified according to the pathological changes which dominated the picture.

HISTOPATHOLOGICAL CLASSIFICATION

Aplasia/hypoplasia of the thymus means a reduced thymic weight due to a development failure. Microscopically a deficiency of the lymphoid component or of both epithelial and lymphoid cells is seen. This condition is always combined with deficiency in the immune capacity (7, 17).

Involution of the thymus is seen in stressful situations (infection, malnutrition, etc.) of more than 24 hours' duration (acute involution) and with advancing age (chronic involution). In the case of acute involution the decrease in thymus weight seems to be steroid mediated. The age involution is probably in some way physiological. A chronic type of involution is also seen in Cushing's disease, due to high levels of corticosteroids. Microscopically, there is a marked numerical reduction of the lymphocytes in the cortex and to a lesser extent in the medulla (10). There is also an increased number of reticulin fibres. In acute involution an increase in the number of cystic Hassall's corpuscles and spindle-shaped cells in the medulla (7) as well as phagocytosis of lymphocytes in the cortex (11) may also be seen.

Hyperplasia of the thymus implies an abnormal increase in thymic weight. Microscopy reveals an essentially normal parenchyma. This condition is seen in thyrotoxicosis (high levels of thyroxin), acromegaly (high levels of growth hormone) and Addison's disease (low levels of corticosteroids) (7, 9). The diagnostic term 'status thymolymphaticus', which was often used formerly when a large thymus was found in cases of sudden death, has now been abandoned. These apparently large thymic glands have in fact been within the normal weight range (7).

Thymitis refers to a chronic inflammatory process of the thymic tissue, with increased numbers of lymphocytes and plasma cells, as well as several secondary lymphoid follicles, in the medulla. The condition is seen in myasthenia gravis (19) and several other probably autoimmune diseases, especially systemic lupus erythematosus (5). In the case of myasthenia gravis the thymus weight and the corticomedullary ratio are normal. In autoimmune systemic diseases the medullary infiltration of lymphocytes and plasma cells are also accompanied by reduced thymic weight, cortical atrophy and aggregates of epithelial cells in the medulla. These changes are attributed to a concomitant stress involution (7).

Table I. *Diagnosis and cause of thymic biopsy*

Diagnosis	Cause of thymectomy or thymic biopsy								Totals
	Mediastinal tumour	Hilus tumour	Pulmonary tumour	Myasthenia gravis	Thoracotomy for other reason	Hyperparathyroidism	Strumectomy	Daniel's biopsy	
Normal thymus	1		1	15	2	13	1	1	34
Thymitis				26			2		28
Thymic cyst	1								1
Thymoma	17	1		4					22
	19	1	1	45	2	13	3	1	85

Genuine simple cysts of the thymus must be distinguished from cystic degeneration within a thymoma, cystic teratomas or lymphatic cysts/lymphangiomas. Genuine cysts of the thymus are lined with cuboidal, flattened or squamous epithelium. They are either unilocular or multilocular and are probably derived from thymic ducts remnants or cystic Hassall's corpuscles (3).

Thymoma is a term which has not been used uniformly.

Numerous more or less subtle classifications have been suggested. In the present context the term is used more as a macroscopic description meaning a neoplastic—benign or malignant—enlargement of the thymus or the thymic lobe. The exact nature of the neoplastic change is described in microscopically adequate diagnostic terms (20).

The above definitions are taken from Goldstein & Mackay (7) and Kalden (13).

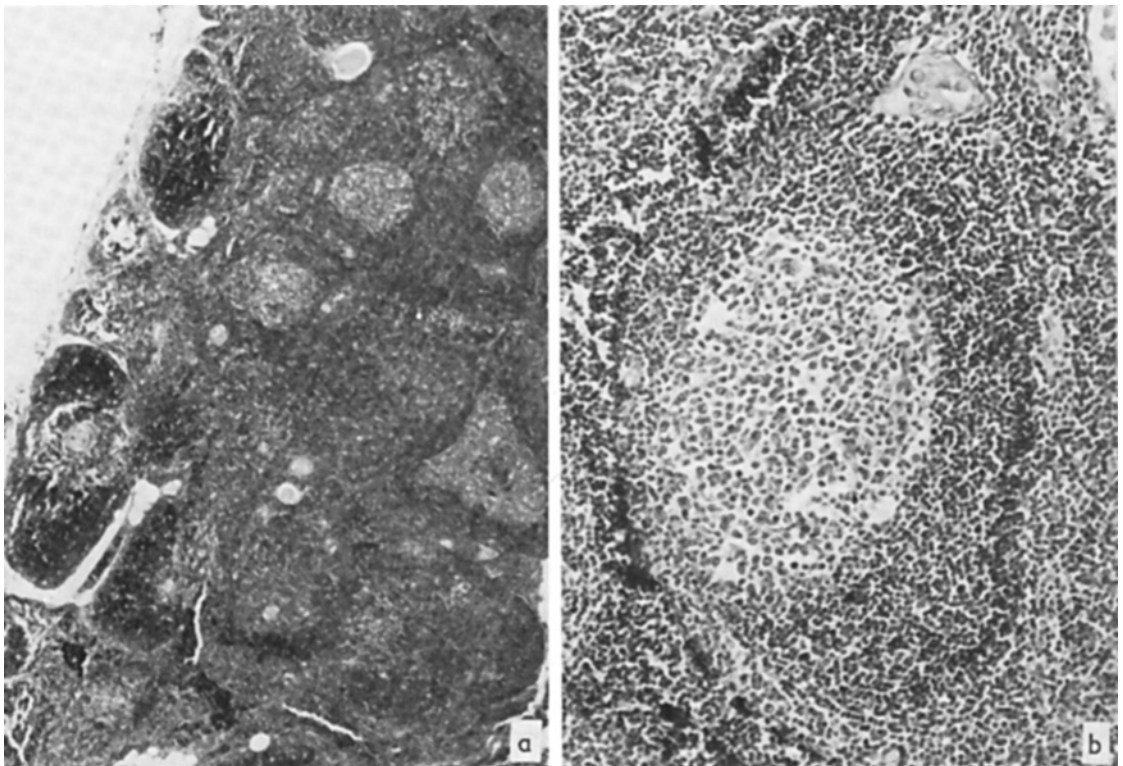


Fig. 1 (a-b). Microphotographs of a thymus removed from an 18-year-old woman with myasthenia gravis. The cortex is involuted. In the medulla, several germinal centres and

infiltration of lymphocytes can be seen. (H.-E., a, $\times 15$; b, $\times 60$.)

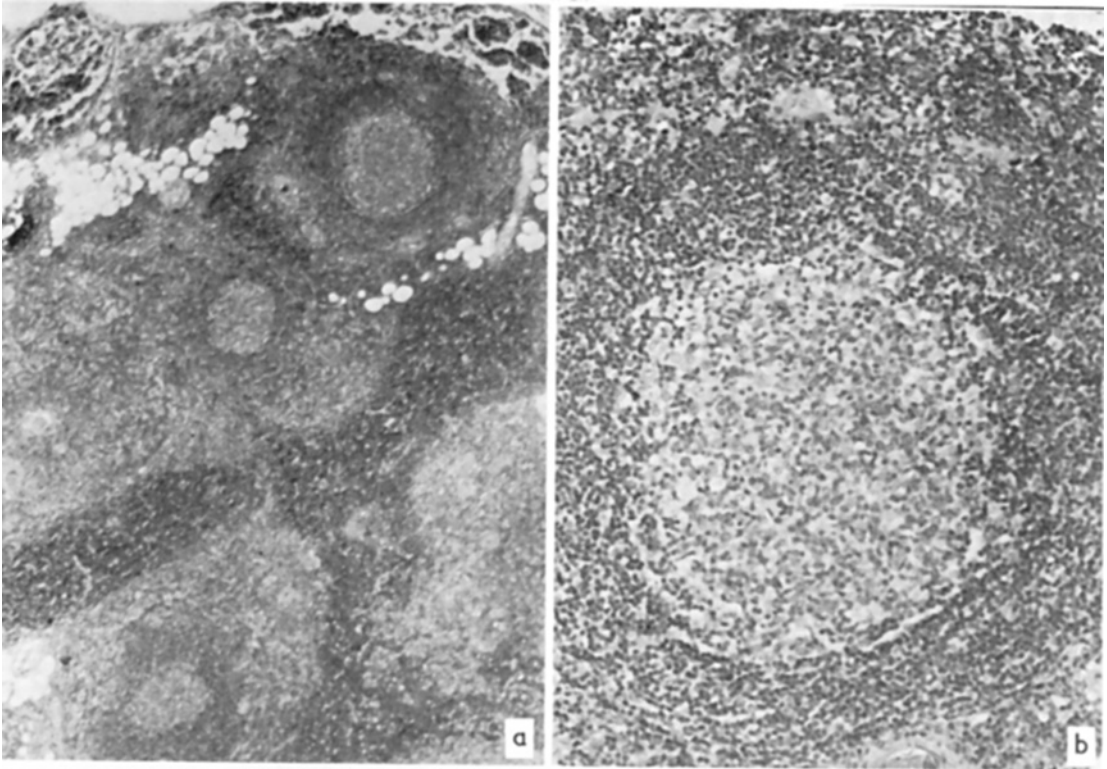


Fig. 2 (a-b). Microphotographs of a thymic biopsy taken during strumectomy in a 25-year-old woman with struma of 4 years' duration; in the last year before operation,

thyrotoxicosis was evident. The cortex is moderately involuted. In the medulla, germinal centres and lymphocyte infiltrates are seen. (H.-E., a, $\times 15$; b, $\times 60$.)

RESULTS

The frequency of different thymic diseases in relation to the reasons for thymectomy or thymic biopsy are summarized in Table 1. The majority of thymectomies (45 cases) were performed on patients with *myasthenia gravis*. In most of these (26 cases or 57%) thymitis was found (Fig. 1). In 33% of the *myasthenia gravis* cases a normal thymus was found, while in four cases (9%) there was a thymoma. In 19 further cases thymectomy was performed because of *suspected mediastinal tumour*; in 17 of these cases a thymoma was found. In 13 cases a biopsy from the thymus, intentional or accidental, was taken *during operation for hyperparathyroidism*. All these biopsies showed normal thymic tissue. In a case with *suspected hilus tumour* a thymoma was found. In one patient operated on for a *suspected pulmonary tumour* a normal thymus was found. In two cases of *thoracotomy performed on other grounds* biopsies from normal thymuses

were taken. In a case of *Daniel's biopsy* normal thymic tissue was obtained. During three *strumectomies* biopsies from the thymus were taken; in one of them a normal thymus was found, while in the 2 other cases thymitis was diagnosed (Fig. 2).

The sex distribution was equal except in the group with *myasthenia gravis* and thymitis, where females predominated. Of the 45 patients with *myasthenia gravis*, 38 were women. Of the 28 patients in whom thymitis was diagnosed, 26 were women.

A few patients (14) were under 20 years of age and a few (15) over 50 years, but the majority (56) were between 21 and 50 years old.

DISCUSSION

For obvious reasons no cases of thymic *hypoplasia* or *hyperplasia* were seen in the material. *Involution*

of the thymus was observed to varying degrees in all non-neoplastic thymus glands. In all cases the involution was of the physiological age-dependent type.

Thymitis-thymoma in myasthenia gravis

In the material discussed here 45 patients with myasthenia gravis were thymectomized. In the majority of these (26 cases or 57%) a thymitis was diagnosed. Three of them were men and the rest women. This female predominance cannot be considered to be fully explained by the usual sex distribution in myasthenia gravis. The death rate, for instance, in this disease has been reported to be about 1.5 times higher for females than for males (14). The female predominance may also reflect the clinicians's indications for thymectomy (15, 18). A thymoma was found in 4 of the 45 patients (9%), one man and 3 women. Of the 15 normal thymuses (33%) found, three were in men and 12 in women.

Several reports have been published concerning the occurrence of thymic disorders in cases of myasthenia gravis. In 35 patients with this disease, Castleman & Norris (2) found 10 (29%) with thymoma and 19 (54%) with germinal centres in the thymic medulla. No germinal centres were found in control cases. In 1966 Castleman (1) summarized the data concerning thymic changes in myasthenia gravis. In 10% a thymoma is present whilst in 72% germinal centres in the thymic medulla are found. The rest have normal thymuses. These data are confirmed by Irvine (12).

In comparison with these figures the incidence of thymitis in myasthenia gravis found in the present study is lower (57%), while that of thymoma is approximately the same.

Of the total number (22 cases) of thymomas in the material only four (18%) were found in patients with myasthenia gravis. In other reports the incidence of myasthenia gravis in patients with thymoma has been considerably higher. Estimations have ranged from 100% (16) to 30% (4). In recent years, however, the estimated figures have decreased considerably, probably due to improved techniques for detecting asymptomatic thymomas, including mass health screening with chest X-ray. The relatively low incidence of myasthenia gravis in cases with thymoma in our material may very well correspond to further improvements in this respect. The varying estimations cited above may also re-

flect differences in the definition of thymoma used by different authors (20).

Thymitis in thyrotoxicosis

Thymus biopsies were obtained from 2 patients with thyrotoxicosis. In both cases thymitis was found. The thymus weights were not noted. The finding of thymic changes in thyrotoxicosis is well established. Hammar (9) found hyperplasia of all components of the thymus in patients with thyrotoxicosis. In addition, germinal centres were found in the thymic medulla in 32% of patients with thyrotoxicosis, but only in 4% of patients with non-toxic goitre (8).

Thymic cysts

One case of simple thymic cyst was included in the material. The cyst was multilocular and lined in some parts with squamous epithelium and in other parts with single-layered cuboid epithelium. In the cyst wall small areas of normal thymic tissue containing Hassall's corpuscles were seen. Data concerning this patient are published elsewhere (21).

Thymomas

Twenty-two cases (26%) of thymoma were found in the material. As mentioned above, four of these thymomas were found in patients with myasthenia gravis. The others were either detected in patients suffering from respiratory distress or diagnosed on routine chest X-rays. An analysis of this material is reported elsewhere (20).

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