

Surgical pathology of the thymus: 20 years' experience

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ABSTRACT Fifty five patients underwent thymic surgery at Papworth Hospital from April 1964 to March 1984. The number presenting and the percentage with symptoms annually remained unchanged during this period. Forty four of these 55 patients had tumours. Twenty eight had thymomas (18% of whom had myasthenia gravis and 7% red cell aplasia), nine Hodgkin's disease, four germ cell tumours, and three secondary carcinomatous tumours. Five tumours were cystic. Six further patients had non-tumourous cystic lesions (four simple, one foregut, one lymphangiectatic). The remaining five patients had follicular hyperplasia; all of these had myasthenia gravis. Complete excision was performed in 41 of the 55 patients. So far survival is 100% in those with benign lesions other than benign thymomas, where the survival was 70% at five years. Those with malignant thymomas had a 60% survival rate at five years and those with Hodgkin's disease 29%.

The thymus, predominantly a third pharyngeal pouch derivative, rarely requires surgery. Since Weigart¹ showed an association between myasthenia gravis and thymoma in 1901, many clinical syndromes have been linked with thymic pathology and attention has been focused on these associations, so that there have been few studies of the whole spectrum of thymic disease.²⁻⁵ For this reason we undertook a retrospective study of all patients with thymic disease managed surgically over 20 years.

Methods

All patients having thymic surgery from 1 April 1964 to 31 March 1984 were included in this study. The pathology was assessed by one of us (PGIS) throughout this period. The case notes of the patients were used to obtain the details of the mode of presentation, diagnosis, surgical treatment, and histology of the excised thymus. The long term outcome was assessed by the patient's survival, evidence of recurrence of symptoms, thymic disease, and development of possible associated syndromes. These data were collected from the hospital notes, the records of other departments into whose care the patients had been transferred, and a questionnaire sent to the patient's general practitioner. Patients were classified according to their pathology, on the

basis of the classification proposed by Rosai and Levine²: A Hyperplasia: true; follicular. B Tumour: thymoma—benign (encapsulated and non-invasive); malignant (non-encapsulated, locally or distantly invading); lymphoma (Hodgkin's or non-Hodgkin's); secondary carcinomatous tumour; germ cell tumours (teratoma, seminoma, dermoid cyst); thymolipoma; carcinoid. C Cysts: simple; developmental; tumours; Hassall's corpuscles. D Other: tuberculosis, hydatid, eosinophilic granuloma, spontaneous thymic haemorrhage.

Results

Fifty five patients underwent thymic surgery during the period of study and the pathological findings are summarised in table 1. Most of the lesions were tumours (44/55), 28 (54%) of which were thymomas; half of these were malignant. Five patients had cyst formation within their tumours (two benign thymomas, three germ cell tumours). Nine had Hodgkin's disease and three secondary thymic tumours. Follicular hyperplasia occurred in five patients. No true thymic hyperplasia was seen. Six patients had cystic lesions (four simple, one foregut, one lymphangiectatic).

MODE OF PRESENTATION

The number of patients presenting annually was small (mean 2.75, range 0-7 a year) and changed little with time (fig 1). Thirty six patients (66%) had symptoms at presentation. In general, symptoms were more

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Accepted 29 July 1985

Table 1 Details of patients and presenting symptoms

Pathology	No of patients	Age (y), mean (range)	% male	No (%) with symptoms at presentation	Symptoms
Hyperplasia					
True	—	—	—	—	—
Follicular	5	28 (18–43)	20	5 (100)	Myasthenia gravis (5)
Tumours					
Thymoma—malignant	14	51 (8–77)	71	10 (71)	Anterior chest pain (4), SOBE (2), cough (2), lump in neck (1), hoarseness (1)
benign	14	48 (26–58)	56	9 (62)	Myasthenia gravis (5), SOBE (2), cough (2)
Lymphoma—Hodgkin's	9	35 (16–44)	56	7 (78)	Lump in neck (5), SVC obstruction (1), anorexia (1)
non-Hodgkin's	—	—	—	—	—
Germ cell	4	30 (18–49)	50	1 (20)	Lump in neck (1)
Secondary tumour	3	62 (58–63)	100	3 (100)	SVC obstruction (1), hoarseness of voice (1), cough (1)
Cysts					
Non-tumours	6	45 (19–77)	50	1 (17)	Lassitude (1)
Total	55				

SOBE—Shortness of breath on exertion; SVC—superior vena cava.

commonly found in patients with malignant disease, although all five patients with follicular hyperplasia had myasthenia gravis. Five further patients with benign thymomas had myasthenia gravis and two (one with malignant thymoma and the other with benign thymoma) had red cell aplasia. There was a slight male preponderance overall, which was more pronounced in those patients with malignancies. On the other hand, myasthenia gravis was more common in women (table 1). Younger patients tended to have follicular hyperplasia; secondary tumours were more common in the older age group (table 1).

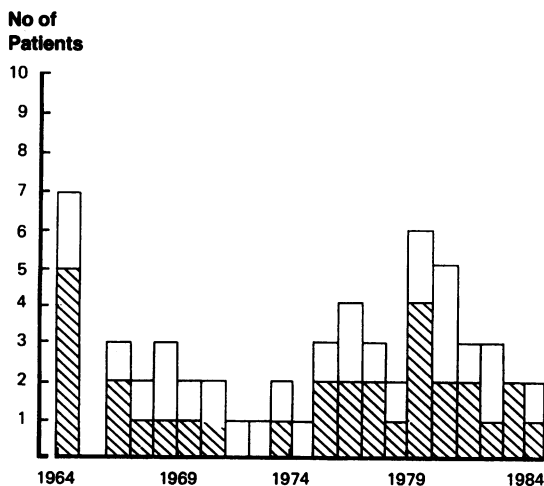


Fig 1 Numbers of patients undergoing thymic surgery annually at Papworth Hospital, 1964–84. □ Symptomless at presentation; ▨ with symptoms at presentation.

INVESTIGATIONS

Chest radiographs or tomograms showed an anterior mediastinal mass in 32 patients. Conventional linear tomography was replaced by computed tomography in 1981.

TREATMENT

The surgical approach did not change over the study period. Median sternotomy was performed in 23 patients and was used in all who had a preoperative planned total thymectomy or myasthenia gravis. Complete excision of the area of thymic disease was possible in 41 patients. Fourteen cases had incomplete resection, six with malignant thymomas, four with Hodgkin's disease, two with secondary carcinoma, and two with benign thymomas. All patients with malignant thymomas or incompletely excised benign thymoma underwent postoperative radiotherapy. Three patients with metastases from malignant thymomas had cytotoxic treatment in addition. Patients with Hodgkin's disease had standard treatment appropriate to the stage of their disease (seven had stage 3 or 4 disease). Histologically there were seven cases of the nodular sclerosing subtype and one case each of the lymphocyte depleted and lymphocyte predominant variants.

SURVIVAL

Thirty six of the 55 general practitioners responded to the questionnaire. Survival of the patients with thymomas and Hodgkin's disease is shown in figure 2. At five years, of the patients who had had malignant thymomas, there was no significant difference in survival between those treated by total excision alone and those treated by incisional biopsy and

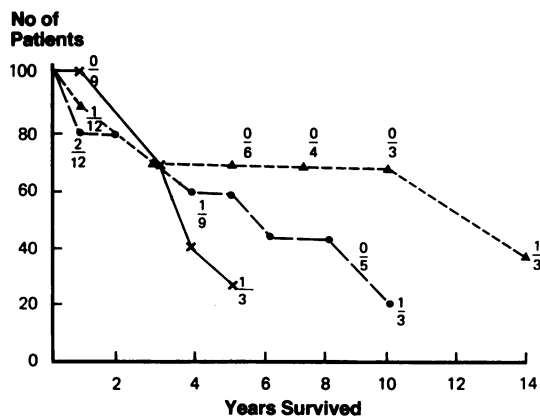


Fig 2 Actuarial survival of patients with benign thymoma (▲—▲), malignant thymoma (●—●), and Hodgkin's lymphoma (x—x).

$$\frac{0}{9} = \frac{\text{No of deaths in the year}}{\text{No of patients entering the year}}$$

radiotherapy. Four patients with myasthenia gravis and thymoma survived. One patient with follicular hyperplasia and myasthenia gravis was lost to follow up at seven years and a second, having survived 15 years, died of a chest infection complicating prostatectomy. All myasthenic patients continued to require their preoperative anticholinesterase treatment, despite surgery. Both patients with red cell aplasia died, one with malignant thymoma at two months from metastatic disease and one with benign thymoma at eight months from a chest infection. Both required frequent transfusions after complete thymectomy. No patient who had undergone thymic surgery in this study subsequently developed symptoms of a previously described clinical syndrome (table 2). Two of the three patients with secondary thymic tumours (all from bronchogenic carcinomas) died within four months of their operation. The third, treated by total excision (pneumonectomy and

thymectomy), is still alive after three years. The 10 patients with germ cell tumours or non-tumourous cystic lesions are all alive.

Discussion

Thymectomy is rarely performed at Papworth Hospital, the annual rate being 2.75 patients per year, representing an incidence of 0.25 per 100 000 of the catchment population. The rate did not change during the study period. A greater proportion of patients underwent thymectomy for hyperplasia in this series than in the 40 year series of Wychulis *et al* reported in 1964,⁵ possibly owing to the increased use of surgery in patients with myasthenia gravis. Bernartz *et al*⁶ in a report of thymic surgery in 1961 showed a steady fall in the incidence of symptoms at presentation in patients with thymic disease. This they attributed to the increased use of routine chest radiography over the course of their study.

Two thirds of the group had symptoms, a proportion that was constant over the 20 years of this study. Symptoms fell into three groups: (1) those arising directly from the thymic lesion either by compression or by invasion—for example, a palpable lymph node, hoarseness of voice, superior vena caval obstruction; (2) those associated with a previously described clinical syndrome (table 2)—for example, the exercise induced weakness of myasthenia gravis and the dyspnoea, fatigue, and shortness of breath of red cell aplasia or the recurrent chest infections, lymphadenopathy, enterocolitis, and sinusitis of hypogammaglobulinaemia; (3) non-specific systemic symptoms such as anorexia and lassitude. Symptoms were more common and tended to be specific to the thymic lesion in those with malignancy. Patients with thymic cysts and germ cell tumours had symptoms least frequently. Previously described clinical syndromes (table 2) appeared in seven of the 28 patients with thymoma but in no other cases, although such syndromes have been reported in association with other thymic disease.⁴ Myasthenia gravis occurred in 18% of patients with thymoma, all of which were benign. A variable incidence, rising as high as 46%, with no relationship to malignancy has been previously reported.⁶ Two patients with thymoma (7%) had red cell aplasia, a proportion previously noted,⁴ and both required frequent transfusions after operation. Kranz and Kow⁷ identified a gamma globulin fraction inhibiting haemopoiesis in red cell aplasia. Myasthenia and red cell aplasia associated with thymoma have a prognosis dependent on the thymoma itself. Twenty two per cent of the patients with malignant thymomas in this series had metastases (to lymph nodes, adrenal, chest wall, brain, and bone marrow), a similar proportion to that reported by Cohen *et al*.¹⁰

Table 2 Clinical syndromes associated with thymoma^{2 7 8 12}

Autoimmune

Myasthenia gravis, polymyositis (with or without myocarditis), systemic lupus erythematosus, pemphigus, Sjögrens syndrome, lupoid hepatitis, rheumatoid arthritis, scleroderma, Hashimoto's thyroiditis, vasculitis

Haematological

Red cell aplasia, hypogammaglobulinaemia, myeloma, acute leukaemia, hypogammaglobulinaemic purpura, erythrocytosis, megakaryocytopenia

Endocrine

Cushing's syndrome associated with carcinoid tumour of thymus, thyrotoxicosis

Miscellaneous

Megaesophagus, peripheral neuropathy, Kaposi's sarcoma, chronic mucocutaneous candidiasis

Metastases had previously been reported as rare.⁵ Rosai and Levin² found that only 7% of their patients with thymoma had malignant change, but in other reviews^{10 11} there is an incidence similar to ours. It is unlikely that thymic malignancy is becoming more common; the small numbers of cases in these reviews^{2 10 11} are probably responsible for the variation.

All the patients with cystic lesions and germ cell tumours have survived. Five year actuarial survival rates of 70% and 60% for benign and malignant thymomas respectively is similar to those of recent reports.^{9 10} A 29% actuarial survival of patients with Hodgkin's disease was unexpectedly low, as it has been shown that thymic tumours are common in patients with Hodgkin's disease and do not affect prognosis.¹³ This poor survival is difficult to explain as the clinical details are similar to those of the patients in other series.⁴ Secondary malignant disease may not indicate a poor prognosis. In our series there were only three such patients, one of whom is still alive three years after complete excision of the thymic secondary and bronchogenic primary tumours. Thymic metastases from primary carcinomas (gastric, bronchogenic, and laryngeal) have been shown to occur commonly.¹⁴

We would like to thank Mr BB Milstein for allowing us to include his patients in this review and Rachel Sinfield and Jane Irvine for their secretarial work.

References

1 Weigart C. Pathologisch-Anatomische Beitrag zur eibs-

- chen Krankheit (Myasthenia gravis). *Neurol Centralb* 1901;**20**:597-601.
- 2 Rosai J, Levine GD. *Tumour of the thymus: atlas of tumour pathology*. Second series, fasc 13. Washington DC: Armed Forces Institute of Pathology, 1976.
- 3 Sabiston DC jun, Scott HW jun. Primary tumours and cysts of the mediastinum. *Ann Surg* 1952;**136**:777-9.
- 4 Oldham HN, Sabiston DC jun. Primary tumours and cysts of the mediastinum. *Monogr Surg Sci* 1967;**4**:243-79.
- 5 Wychulis AR, Payne WS, Claget OT, Woolner LB. Surgical treatment of mediastinal tumours. A forty year experience. *J Thorac Cardiovasc Surg* 1971;**62**:376-92.
- 6 Bernartz PE, Harrison EG, Claget OT. Thymoma: a clinico-pathologic study. *J Thorac Cardiovasc Surg* 1961;**42**:424-44.
- 7 Kranz SB, Kow B. Studies on red cell aplasia. 1. Demonstration of a plasma inhibitor to haeme synthesis and an antibody to erythroblast nuclei. *Proc Natl Acad Sci USA* 1967;**58**:493-500.
- 8 Goldstein G, Mackay IR. Thymic tumours and systemic disease associated with thymoma. In: Warren H, Green I, eds. *The human thymus*. St Louis: CV Mosby, 1969: 194-227.
- 9 Shamji F, Pearson FG, Todd TRJ, Ginsberg RJ, Ilves R, Cooper JD. Results of surgical treatment for thymoma. *J Thorac Cardiovasc Surg* 1984;**87**:43-7.
- 10 Cohen DJ, Ronnigen LD, Graeber GM, et al. Management of patients with malignant thymoma. *J Thorac Cardiovasc Surg* 1984;**87**:301-7.
- 11 Castleman B, Norris EM. The pathology of the thymus in myasthenia gravis. A study of 35 cases. *Medicine* 1949;**28**:27-58.
- 12 Lewis BD, Hurt RD, Spencer-Payne W, Farrow GM, Knapp RH, Muhm JR. Benign teratomas of the mediastinum. *J Thorac Cardiovasc Surg* 1983;**86**:727-32.
- 13 Marshall AHE, Wood C. The involvement of the thymus in Hodgkin's disease. *J Pathol* 1967;**73**:163-6.
- 14 Middleton G. Involvement of the thymus by metaplastic neoplasia. *Br J Cancer* 1966;**20**:41-6.

bronchial challenge testing in our study of the prevalence of asthma. In commenting on our finding that over one quarter of children had a history of current or past wheeze, they state that "clearly, not all of these children had asthma." What did they have? Many but not all of these children showed increased airway responsiveness, as did a proportion of those with a history of dry cough. If, as advocated by Woolcock and colleagues,² asthma is diagnosed only when symptoms are accompanied by demonstrable airway hyperresponsiveness, much past asthma, and even mild current asthma, will not be diagnosed. Perhaps our problem is the use of the word "asthma." We can demonstrate and measure degrees of bronchial responsiveness, and we can obtain and clinically categorise a history of wheezing or cough. While symptoms and hyperresponsiveness are often found together, they are not synonymous, and neither is exactly equivalent to variable airflow obstruction, which is the hallmark of asthma. We should report both the history of symptoms and the degree of airway responsiveness rather than use their dual presence to make a diagnosis of a condition whose precise definition continues to elude us.

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- 1 Juniper EF, Frith PA, Hargreave FE. Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. *Thorax* 1981;**36**:575-9.
- 2 Britton WJ, Woolcock AJ, Peat JK, Sedgwick CJ, Lloyd DM, Leeder SR. Prevalence of bronchial hyperresponsiveness in children. The relationship between asthma and skin reactivity to allergens in two communities. *Int J Epidemiol* (in press).

Book notices

Recommended Health Based Limits in Occupational Exposure to Selected Mineral Dusts (Silica, Coal). WHO Study Group 734. (Pp 82; Sw Fr 12.) Geneva: World Health Organisation, 1986. ISBN 92 4 120734 5.

This report is the latest of a series of publications produced by groups of experts for the World Health Organisation. Its object is to make recommendations for exposure limits to fibrogenic mineral dusts, including coal and silica. The group initially defines pneumoconiosis and details the factors that influence the retention and elimination of airborne particles in the respiratory tract and their eventual fate. The methods of measuring airborne particulates are clearly described. Subsequent sections describe the pathology, pathogenesis, clinical manifestations, and complications of silicosis and coalworkers' pneumoconiosis. The published evidence relating exposure to dust and the development of pneumoconiosis is comprehensively reported. The group finally makes recommendations of exposure limits for free crystalline silica and coalmine dust and regarding the surveillance of the workers and their environment. This publication is short and easy to read. It provides comprehensive current information on two of the pneumoconioses with appropriate references. It is recommended for those practitioners directly concerned with this industry.—CACP

Inhaled Aerosol Bronchodilators. ER McFadden jun. (Pp 122; £25 softback.) Baltimore: Williams and Wilkins, 1986. ISBN 0-683-05867-3.

This is a small, compact paperback which, although primarily about aerosols and delivery systems, covers many aspects of drug therapy in the treatment of diseases of airflow obstruction. The book is unusual in that it has no foreword by the author, and thus leaves the reviewer undecided on the audience the author intended to reach—a problem exacerbated when he is reviewing North American publications for British readers and not entirely resolved after it has been read in its entirety. The history of inhalation therapy is reviewed, and followed by an excellent chapter on aerosols, their deposition and generation. This is followed by a discourse on the pharmacokinetics of inhaled substances, which does highlight the present paucity of data on bronchodilators. Patients' and doctors' errors in the use of hand held aerosols and means of overcoming such problems are well described. Metabolism, structure, and function followed by pharmacology make up the major portion of the book, but the inherent safety of selective β stimulants is also covered. Drug dose differences between the various delivery systems are highlighted. The vexed problem of bronchial tachyphylaxis to selective β stimulants is reviewed, and sensibly dismissed as of little clinical relevance in asthmatics. The remainder of the book deals with drug interactions and specific problems such as aerosol use in pregnancy and exercise induced asthma. The book is clearly written, remarkably readable, and illustrated clearly and mainly appropriately. The bibliography is up to date and extensive, suggesting that the author is aware of the limited readership. I believe that the book should be read by all medical students and general practitioners, but it is probably of less interest to the specialist thoracic physician. The bibliography, however, extends the readership to all trainee thoracic physicians. I am pleased to have the book for the undergraduate and postgraduate library, but at £25 it is an expensive book for the solitary purchaser.—GMC

Correction

Surgical pathology of the thymus: 20 years' experience

We have learned of the following errors in the references to the paper by Mr S Large and colleagues (January 1986; **41**:51-4). Reference 5 should read: Wychulis AR, Payne WS, Clagett OT, Woolner LB. Surgical treatment of mediastinal tumours. A forty year experience. *J Thorac Cardiovasc Surg* 1971;**62**:379-92. It is stated in error in the text that this work was published in 1964. In reference 6 "Clagett" should read "Clagett."