Giant thymic carcinoid

L.C.H. John, P. Hornick, S. Lang¹, J. Wallis and S.J. Edmondson

Departments of Cardiothoracic Surgery and ¹Pathology, St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK.

Summary: Thymic carcinoid is a rare tumour. It may present with ectopic endocrine secretion or with symptoms of compression as a result of its size. A case is reported which presented with symptoms of compression where the size of the tumour was uniquely large such as to warrant the term giant thymic carcinoid. The typical histological features are described, together with its possible origin and its likely prognosis.

Introduction

A case of thymic carcinoid is presented in this report which we believe to be uniquely large. It demonstrates the size to which these tumours may grow when not endocrinologically active and illustrates that it is not the tumour mass in carcinoid tumours that appears to be the determinant as to their endocrine activity.

Case report

A 53 year old male was referred with a one month history of dyspnoea and cough. Clinical examination was unremarkable. A chest radiograph showed a large anterior, lobulated mass, extending to the right lateral chest wall. This was associated with a right sided pleural effusion. Full blood count, urea and electrolytes, and liver function tests were normal.

The pleural effusion was aspirated with some improvement in symptoms. The aspirate was bloodstained and cytology failed to show the presence of malignant cells.

'Tru-cut' biopsy of the mass and subsequent histology indicated that it was a carcinoid tumour. As a result the patient underwent liver ultrasound and urinary 5 HIAA (hydroxy-indole acetic acid) screening test, the results of which were both negative. A thoracic computed tomographic (CT) scan (Figure 1) demonstrated a large mass in the anterior mediastinum extending into the right hemithorax.

The patient underwent resection of the tumour which was approached via a median sternotomy. The anterior mediastinum was occupied by a

Figure 1 Thoracic CT scan of tumour prior to excision.

lobulated tumour which extended into the right hemithorax, causing right upper lobe compression and right lower lobe collapse. Vascular pedicles from the tumour drained to the brachiocephalic vein. There was no evidence of invasion of the surrounding structures and after entering the right pleural space the tumour could be fully mobilized and delivered into the wound.

The patient made an uneventful recovery from the operation and was discharged on the sixth post-operative day with complete resolution of the presenting symptoms.

Histopathology

The surgical specimen was a large 23.5 × 19.5 × 11.5 cm, lobulated, well circumscribed tumour

weighing 3,270 g. On cut surface the tumour showed an homogeneous pale appearance with focal small haemorrhagic areas.

Histologically the tumour consisted of polygonal cells with oval or round nuclei and an eosinophilic granular cytoplasm (Figure 2), often arranged in trabeculae. Scattered mitotic figures were present, up to 4 per 10 high power fields; however, there was minimal necrosis.

The tumour cells showed argyrophilic histochemical staining properties and were positive for neuroendocrine immunohistochemical markers [protein gene product (PGP) 9.5 and neurone specific enolase] (Figure 3).

Ultrastructural examination showed numerous cytoplasmic membrane bound neurosecretory granules, confirming the diagnosis of thymic carcinoid tumour (Figure 4).

Discussion

Thymic carcinoid is a rare tumour with fewer than 100 cases reported.¹ It has only relatively recently been recognized as a distinct pathological entity, being clearly differentiated from a thymoma (the most common anterior mediastinal tumour) by Rosai and Higa in 1972.²

A major feature on light microscopy, differentiating thymic carcinoid tumours from thymomas, is the absence of lymphocytes whose presence is a major feature of the latter. Occasionally on light microscopy thymic carcinoids may appear spindly or pleomorphic, in which case they become less distinguishable from lymphocyte-poor thymomas. Immunoperoxidase studies or electron microscopy are helpful. The ultrastructural hallmark of thymic carcinoid is the presence of dense-cored neurosecretory granules on electronmicroscopy. These are typically of 100–300 nm diameter with a dense core surrounded by a loose fitting membrane.³ Other electron microscopic features of thymic carcinoid include the lack of basement membrane material, cytoplasmic processes, desmosomal junctional complexes and type 1 microfilaments, together with the presence of irregular nuclear contents, easily discernible smooth endoplasmic reticulum, perinuclear whorls of type 2 microfilaments, lysosomes that are occasionally prominent and rudimentary cilia.^{4,5} On immunohistochemical analysis, no single conventional marker protein has proved to be a specific diagnostic aid for thymic carcinoid.⁶ However, positive reactions for the neuroendocrine immunohistochemical markers, such as PGP 9.5 and neurone specific enolase (as there were in this case), supports the

Figure 2 Histological appearance of tumour. Note mitotic figures in the centre of the field (H&E $\times 600$).

Figure 3 Tumour cells showing immunoreactivity for the neuroendocrine marker PGP 9.5 ($\times 375$).

Figure 4 Electronmicrograph showing several cytoplasmic membrane bound dense core neurosecretory granules (arrowheads). Desmosomal junctions are also seen (arrows) ($\times 36,000$).

neuroendocrine nature of the tumour.

The origin of thymic carcinoid tumour is believed to be the same as that of other carcinoid tumours, arising from neuroendocrine cells. These are a related, though not identical group of cells variously named Kultschitsky, argentaffin, argyrophil, chromaffin or yellow cells. Their presence in the normal thymus is easily shown in some species.^{7,8} In humans these are more scarce and of argyrophilic, non-argentaffin type only.⁹ Koss has demonstrated the presence of cells containing neurosecretory granules in the normal human thymus on electron microscopy.¹⁰ The embryological origin of these cells is disputed. Bensch *et al.*¹¹ stated that they were present in all structures derived from the primitive endodermal canal including derivatives of the pharyngeal arches, tracheobronchial tree, gastrointestinal tract, pancreatic and bile ducts. Others have described their origin as being from the neural crest (i.e. from

neuroectoderm) which is also the case if they are regarded as arising from APUD cells. Pearse and Takor¹² have suggested that the neuroendocrine population of the gut and pulmonary systems may be derived from a neuroendocrine programmed ectoblast. Alternatively, the neuroendocrine cells may have more than one potential origin. Wick *et al.*¹³ have described two histological variants of thymic carcinoid and have suggested that the origin of one is from neuroendocrine cells of endodermal origin and the other from neuroectodermal origin.

Thymic carcinoid may present in the following ways: (i) Endocrinologically active (almost half in the series of Wick *et al.*¹³) most commonly presenting as Cushing's syndrome or rarely as part of multiple endocrine neoplasia syndrome. (ii) Non-specific systemic symptoms such as fatigue, fever and night sweats.¹⁴ (iii) Asymptomatically on routine chest X-ray. (iv) Intrathoracic pressure symptoms, as with the case presented here.

No case of thymic carcinoid has been reported as being associated with the carcinoid syndrome. It has been suggested that the syndrome maybe related to the size of the tumour,¹⁵ though such is clearly not the case, in view of its absence in this reported case, with such a large tumour. It is probable that the absence of carcinoid syndrome in these tumours is because they are not very active, that is they do not secrete sufficient vasodilating peptides or 5-hydroxytryptophan.

Thymic carcinoids generally have a poorer prognosis than other carcinoid tumours. Of the 15 cases in the Wick series,¹³ of which 11 underwent surgery, only one patient was tumour free at more than 5 years follow-up. Eleven (73%) developed metastases (most commonly skin and bone) and had a mean survival of 3 years following the diagnosis of extrathoracic metastases. It has been suggested that the poorer prognosis for thymic carcinoid compared to other carcinoids may be related to their site often resulting in a relatively large tumour (if endocrinologically inactive) before causing symptoms. This is illustrated in an extreme form in the reported case. However, it is known that the endocrinologically active thymic carcinoids which are smaller than the inactive¹³ have a poorer prognosis.

Surgical excision with complete clearance is the treatment of choice. There is some contention as to whether postoperative radiotherapy or chemotherapy is of benefit. In the Wick series¹³ the overall cure rate (5 year tumour-free survival) for all treatments in patients with at least a 5 year follow-up period, was 13% (1 of 8). The response to adjuvant treatment was hardly better (1 of 7).

References

1. Wick, M., Scott, R., Li, C. & Carney, J. Carcinoid tumour of the thymus. A clinicopathologic report of seven cases with a review of the literature. *Mayo Clin Proc* 1980, **55**: 246–254.
2. Rosai, J. & Higa, E. Mediastinal endocrine neoplasm of probable thymic origin, related to carcinoid tumour: clinico-pathologic study of 8 cases. *Cancer* 1972, **29**: 1061–1074.
3. Blom, P. & Johannessen, J.V. Mediastinal mass in a young male. *Ultrastruct Pathol* 1983, **4**: 391–395.
4. Rosai, J. & Levine, G.D. Tumours of the thymus. In: *Atlas of Tumour Pathology*, series 2, fascicle 13. Armed Forces Institute of Pathology, Washington D.C., 1976.
5. Wick, M.R. & Scheithauer, B.W. Thymic carcinoid: A histologic, immunohistochemical, and ultrastructural study of 12 cases. *Cancer* 1984, **53**: 475–484.
6. Herbst, M.W., Kummer, W., Hofmann, W., Otto, H. & Heym, C. Carcinoid tumours of the thymus: an immunohistochemical study. *Cancer* 1987, **60**: 2465–2470.
7. Hakanson, R., Larsson, L.I. & Sundler, F. Peptide and amine producing endocrine-like cells in the chicken thymus: a chemical, histochemical and electron microscopic study. *Histochemistry* 1974, **39**: 25.
8. Toro, I., Olan, I., Rohlich, P. & Viragh, S. Electron microscopic observation on myoid cells of the frogs' thymus. *Anat Rec* 1969, **165**: 329–342.
9. Vetter, J.M. & Macadam, R.F. Fine structural evidence for hormone secretion by the human thymus. *J Clin Pathol* 1973, **26**: 194–197.
10. Koss, L.G. In Discussion of case 3, specialty slide conference in Surgical Pathology, *59th Annual Meeting of the International Academy of Pathology*, St. Louis, MO., March 10, 1970.
11. Bensch, K.G., Corrin, B., Pariente, R. & Spencer, H. Oat cell carcinoma of the lung. Its origin and relationship to bronchial carcinoid. *Cancer* 1968, **22**: 1163.
12. Pearse, A.G.E. & Takor, T. Embryology of the diffuse neuroendocrine system and its relationships to the common peptides. *Fed Proc* 1979, **38**: 2288.
13. Wick, M.R., Bernatz, P.E., Carney, J.A. & Brown, L.R. Primary mediastinal carcinoid tumours. *Am J Surg Pathol* 1982, **6**: 195–205.
14. Levine, G.D. & Rosai, J. Thymic hyperplasia and neoplasia: a review of current concepts. *Hum Pathol* 1978, **9**: 495–514.
15. Deneffe, G. & Moerman, P. Carcinoid tumour of the thymus: a case report. *Acta Chir Belg* 1986, **86**: 72–74.