CASE REPORT

Primary neuroendocrine carcinoma of the thymus

Gajanan S. Gaude, Virupakshi Hattiholi[1], Prakash R. Malur[2], Jyothi Hattiholi

Departments of Pulmonary Medicine, [1]Radiodiagnosis, Imaging and [2]Pathology, J. N. Medical College, Belgaum, Karnataka, India

Address for correspondence:
Dr. Gajanan S. Gaude, Department of Pulmonary Medicine, K. L. E. University's, J. N. Medical College, Belgaum, Karnataka, India.
E-mail: gsgaude922@gmail.com

ABSTRACT

Primary neuroendocrine tumors of the thymus, previously known as carcinoid tumors of the thymus, are unusual and rare tumors, and prognosis for these patients has been difficult to predict. We hereby report a case of primary neuroendocrine tumor of the thymus that had an aggressive and fatal course in spite of surgical resection and adjuvant chemotherapy. These tumors must be regarded as a malignant neoplasm that is prone to metastasize to distant sites, even after total excision.

Key words: Carcinoid tumor, mediastinum, neuroendocrine carcinoma, thymus

INTRODUCTION

Thymomas constitute majority of the thymic neoplasms. In contrast. thymic neuroendocrine carcinoma is a distinct clinicopathologic entity and extremely rare. It is a potentially malignant tumor and often develops distant metastases, sometimes after long intervals.[1] However, the behavior of this unusual tumor is unpredictable,[2] and there has been no satisfactory classification system to predict its progression. We hereby report a rare case of primary neuroendocrine carcinoma of the thymus which had an aggressive behavior and died within five months.

CASE REPORT

A 47 years old male presented with chest pain and gradually progressing dyspnoea (MRC Grade III) of three months duration. He was a labourer and a non smoker with no history of exposure to any occupational or inorganic dusts. The chest pain was dull aching and mainly localized in left axillary region with no radiation and not related to the meals. He was also having cough with mucoid expectoration. There was no hemoptysis. Examination revealed averagely built person with BMI of 20, and no clubbing and lymphadenopathy. Respiratory system examination revealed diminished movements and breath sounds on the left hemithorax. Chest radiograph revealed a uniform density homogenous opacity in the lower left hemithorax with obliteration of the left cardiac border. The mediastinum was shifted to the right side [Figure 1]. CT scan of the thorax revealed a large well defined heterogenous density anterior mediastinal mass. There were some areas of necrosis within the mass. The mass was extending up to the pleural surface, but there was no infiltration of chest wall. There was no involvement of the mediastinal lymph nodes [Figure 2a and b]. Abdominal ultrasonography did not revealed any organomegaly. Routine blood investigations were within normal limits. Serum cortisol levels were within normal levels. Fibreoptic bronchoscopy did not revealed any abnormality. Bronchial washings, bronchial brush biopsy and transbronchial needle aspiration biopsy of the mass were inconclusive. Trans-thoracic tru-cut biopsy of the mass revealed small round tumor cells, but the exact histological diagnosis remained uncertain. As the diagnosis was inconclusive, the patient was taken up for thoracotomy with excision of the tumor. Intra-operatively it was observed that there was a large firm mass in the mediastinum on the left side with invasion of the great vessels. The mass was extending up to the chest wall. Hence, debulking of the tumor was done to the extent possible. Complete excision of the tumor could not be done as it was infiltrating the great vessels and the pericardium. On gross examination, the tumor was uncapsulated, firm, pink-gray mass that was gritty on cut section. Internally there were few areas of necrosis. Histologically, the specimen revealed sheets of pleomorphic spindle shaped cells, with strikingly organoid growth pattern, with insulae, ribbons, festoons, and trabeculae of tumor cells [Figure 3]. In many areas, cellular nests became detached from surrounding fibrovascular septa and foci of central geographic necrosis were present. Immuno-histochemistry of the specimen proved the diagnosis of neuroendocrine carcinoma of the thymus with tumor cells expressing cytokeratin positivity, strong synaptophysin positivity, chromogranin A positivity and

Access this article online	
Quick Response Code:	Website: www.nigeriamedj.com
	DOI: 10.4103/0300-1652.108904

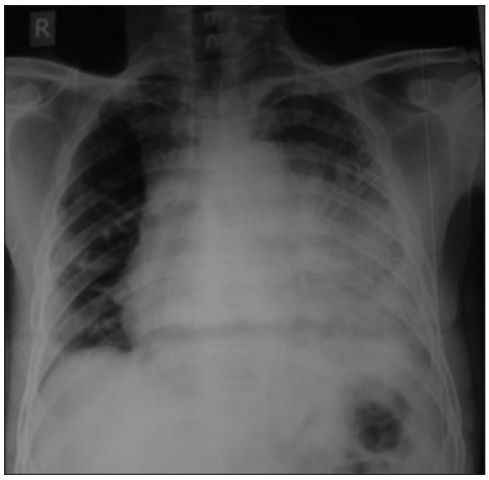

Figure 1: Chest radiograph showing mass in the anterior mediastinum with silhouetting of the left border of the heart

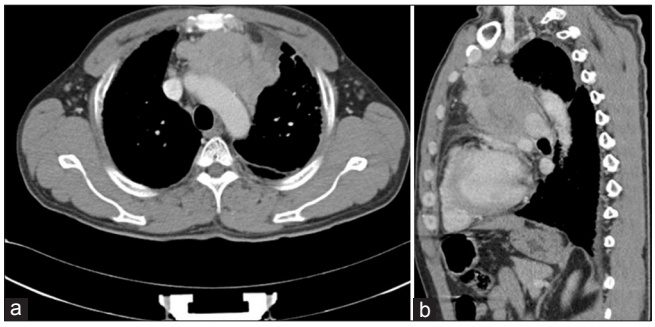

Figure 2: (a) CT scan of the thorax showing non-homogenous mass in the anterior mediastinum with necrosis. (b) Coronal section of the CT scan thorax showing the non-homogenous mass in the anterior mediastinum

TTF-1 positivity [Figures 4-7]. Post-operatively, he received radiotherapy with 4000 rads followed by chemotherapy consisting of Cisplatinum, Bleomycin and Doxorubicin every three weeks for four cycles. But the patient continued to be symptomatic, and his condition worsened over a period of next three months and he died subsequently five months after the diagnosis due to the distant metastasis and recurrence of the disease.

DISCUSSION

Primary neuroendocrine tumors of the thymus, previously known as carcinoid tumors of the thymus, are unusual tumors that account for less than 5% of all anterior mediastinal neoplasms.[3] Primary neuroendocrine tumors of the thymus were first recognized in 1972 by Rosai and Higa.[4] Since then, numerous single case reports and short series of cases have been reported in the literature. Earlier these tumours were known as mediastinal carcinoids, later Gould[5] suggested use of the term neuroendocrinoma for these tumors when they occurred in the thymus. In practice, none of these proposed terms has been adopted fully, and the term thymic carcinoid tumours remains the one most commonly used. Since these tumours have a tendency to follow a more aggressive biologic behavior than their counterparts in other foregut locations, Marana and Suster[6] proposed the designation of thymic neuroendocrine carcinoma for this family of tumors.

The neuroendocrine tumors of thymus have earlier been divided using the similar classification that is used for the neuroendocrine lung tumors, i.e., typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma and small cell carcinoma.[7] The exact proportion of atypical carcinoid among thymic carcinoid tumors is not known, since only a few reports have categorized their tumors as typical or atypical. However, it has recently been argued that the clinical behavior of thymic carcinoids follow a more aggressive course as compared to similar tumors at other locations. Our patient had an aggressive behavior and inspite of wide-excision surgery and adjuvant chemotherapy he succumbed to the recurrence of the disease.

Thymic neuroendocrine carcinoma is of clinical importance as it can be complicated by endocrine abnormalities, either because of adrenocorticotrophic hormone secretion by the thymic carcinoid itself or its association with other endocrine neoplasms.[8] These tumors manifest in one of four ways[9]: (i) they may be asymptomatic, found incidentally on routine chest radiography, (ii) they may produce symptoms of thoracic structure displacement or compression, (iii) they may present with symptoms related to an associated endocrinopathy, or (iv) they may present with symptoms and signs relating to a distant metastasis, most commonly to the liver, lung, pancreas, pleura, and bone. It has been estimated that over one third of patients are asymptomatic and are incidentally discovered.[3] Most patients present with signs and symptoms related to a rapidly expanding mediastinal mass, such as cough, chest pain, and superior vena caval syndrome. At least 20% of affected patients have metastasis at presentation, with the frequency of extra-thoracic metastasis being as high as 20 to 30%.[10] A review of previously reported cases shows that almost 50% of thymic neuroendocrine tumours are functionally active and are associated with endocrinopathies, namely Cushing syndrome in 33 to 40% of affected patients, multiple endocrine neoplasia (MEN) type I (Wermer syndrome) in 19 to 25%, MEN type II (incomplete Sipple's syndrome) in others.[11]

Histologically, the thymic neuroendocrine carcinomas have been divided in three categories: Low-grade (well-differentiated), intermediate-grade (moderately differentiated) and high-grade (poorly differentiated) tumors. Most tumors of thymic origin fall into the category of well differentiated neuroendocrine carcinomas. Moran and Suster[6] after analyzing 80 cases reported that almost 36% of the cases belonged to low-grade variety, 36% belonged to intermediated grade while 19% had high grade

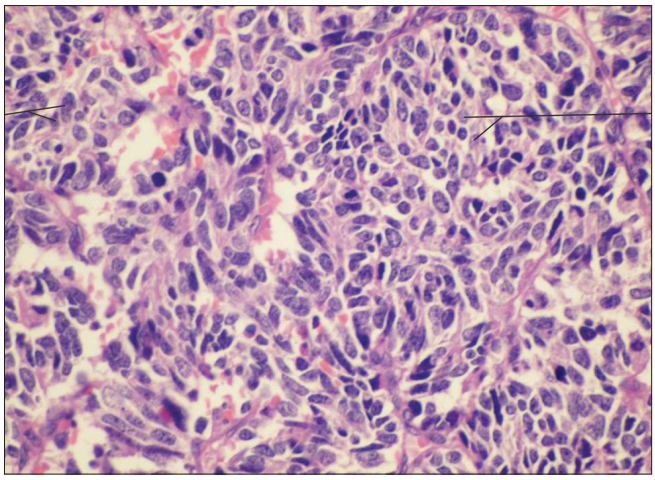

Figure 3: The tumour cells are elongated, nuclei are pleomorphic and are arranged in small, rosette-like acinar structures (H and E, × 40)

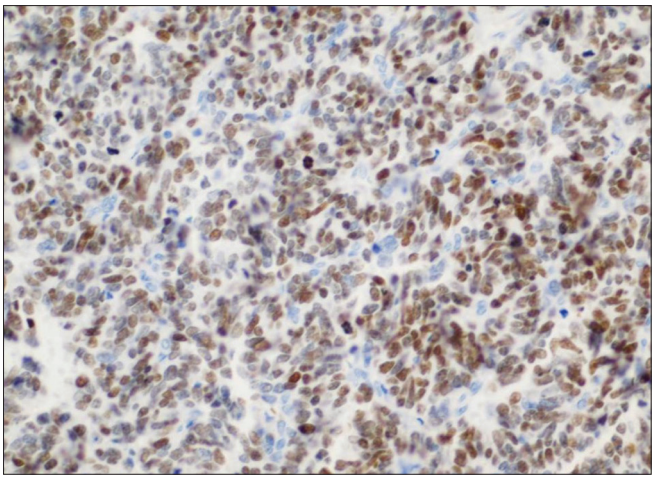

Figure 4: Tumour cells are cytokeratin positive (×40)

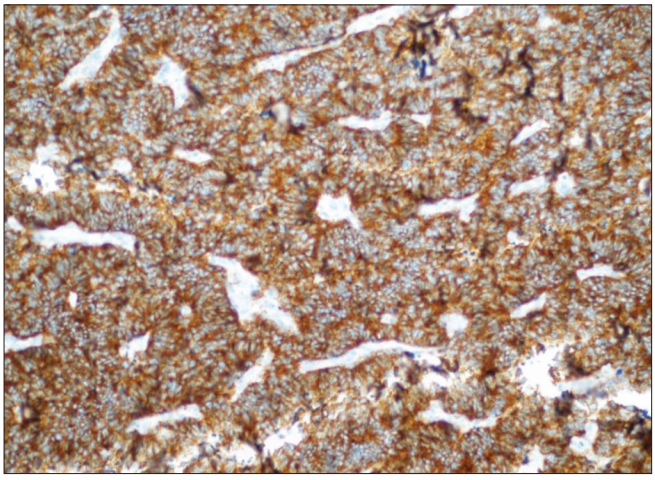

Figure 5: Tumour cells are strongly positive for synaptophysin. Both the cytoplasm and membrane are stained (×40)

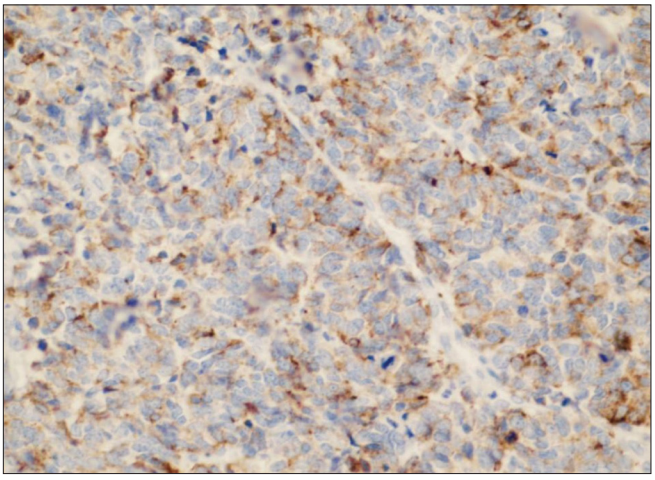

Figure 6: Tumour cells are positive for cytoplasmic chromogranin stain (×40)

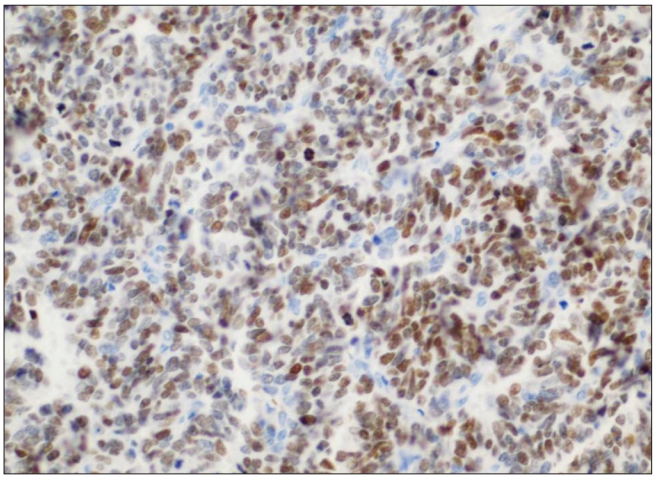

Figure 7: Tumour cells are positive for TTF-1, a cytoplasmic stain

poorly differentiated tumor. The immune-histochemical stains usually provide useful characteristic patterns for thymic neuroendocrine tumors.[1] Thymic neuroendocrine tumors have been demonstrated to express reactivity for cytokeratins in virtually all cases.[12] Markers such as chromogranin, Leu-7, neuron specific enolase, bombesin, and synaptophysin can also help to identify these lesions. Sometimes other markers may also be present in these tumors-melanocyte, serotonin, somatostatin, cholecystokinin, neurotensin, metenkephalin and S-100 protein.

Diagnosis of these thymic endocrinal tumors is difficult, and they manifest as large, lobulated and usually invasive anterior mediastinal masses that may exhibit areas of hemorrhage and necrosis. They are usually indistinguishable from thymomas on plain chest radiograms, although they are usually larger in size. CT scan typically shows a lobulated thymic mass with heterogeneous enhancement and central areas of low attenuation secondary to necrosis or hemorrhage. The differential diagnosis for these lesions includes other primary mediastinal tumors, mainly thymoma, paraganglioma,

lymphoma, parathyroid adenoma or carcinoma, and medullary carcinoma of the thyroid arising in mediastinal location. The most difficult and important differential diagnosis in this setting is with thymoma, particularly of the spindle cell type since they exhibit foci with neuroendocrine appearance due to epithelial pseudo rosettes.[6] Primary neuroendocrine tumors of the thymus as a group appear to be highly aggressive neoplasms. Patients usually die as a result of locally invasive or distant metastatic disease. However, the biological behavior of these tumors may show a direct correlation with the degree of differentiation, with the well-differentiated lesions following a relatively indolent course.[1] Management of these tumors is difficult and challenging. Primary treatment involves the complete resection of the tumor to the extent possible. Recurrent local disease has also to be addressed surgically. Palliative surgical resection or debulking of a large primary tumor causing compression symptoms is indicated in patients with tumor spread to the liver or other organs. Radiotherapy should be considered preoperatively and also following resection, particularly in patients with capsular invasion, because the behavior of these tumors is uncertain and recurrences have been detected several years after initial resection. Whereas the role of adjuvant radiation therapy and chemotherapy is controversial, they have been both used with variable success.[13] Single agents or combination drug therapies with 5-flurouracil, streptozocin, carmustine, VP-16, Cisplatin, and others have been used without any significant impact on the recurrence rate or overall survival.[14] Somatostatin blockers such as Octreotide which is being used in midgut carcinoids tumors, but it has not been systematically used for treating neuroendocrine tumors of the thymus.[15]

The prognosis of patients with primary neuroendocrine thymic tumors remains poor because of the high incidence of local recurrence and metastatic disease after surgical excision. Invasion of local structures is reported in 50% of thymic carcinoids and extra thoracic metastasis in 20-30%.[2] In the present case, there were tumor infiltrations in the great vessels of the thorax and pericardium. Hence complete excision of the tumor was not possible. Prognostic factors that have been shown to impact long-term outcome include the histologic grade of the tumor, the mitotic activity, presence of associated endocrinopathy, capsular invasion, incomplete resection, lymph node status, and presence of metastasis at the time of diagnosis. In one clinical review,[1] it was observed that 51% survived for three years, 27% survived for five years, and 9% survived 10 years or more following extensive surgical excision followed by radiotherapy and chemotherapy.

In summary, primary neuroendocrine tumors of the thymus are aggressive tumors that are associated with poor survival. Surgical resection of the tumor and its extension remains the treatment of choice because the experience with adjuvant therapy has been unsatisfactory.

REFERENCES

1. de Montpréville VT, Macchiarini P, Dulmet E. Thymic neuroendocrine carcinoma (carcinoid): A clinicopathologic study of fourteen cases. J Thorac Cardiovasc Surg 1996;111:134-41.
2. Wick MR, Scott RE, Li CY, Carney JA. Carcinoid tumor of the thymus: A clinicopathologic report of seven cases with a review of the literature. Mayo Clin Proc 1980;55:246-54.
3. Chaer R, Massad R, Evans A, Snow NJ, Geha AS. Primary neuroendocrine tumors of the thymus. Ann Thorac Surg 2002;74:1733-40.
4. Rosai J, Higa E. Mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor. Clinicopathologic study of 8 cases. Cancer 1972;29:1061-74.
5. Gould VE. Neuroendocrinomas and neuroendocrine carcinomas: APUD cell system neoplasms and their aberrant secretory activities. Pathol Annu 1977;12:33-62.
6. Moran CA, Suster S. Neuroendocrine carcinomas (carcinoid tumor) of the thymus. A clinicopathologic analysis of 80 cases. Am J Clin Pathol 2000;114:100-10.
7. Arora R, Gupta R, Sharma A, Dinda AK. Primary neuroendocrine carcinoma of thymus: A rare cause of Cushing's syndrome. Indian J Pathol and Microbiol 2010;53:148-51.
8. Duh QY, Hybarger CP, Geist R, Gamsu G, Goodman PC, Gooding GA, *et al*. Carcinoids associated with multiple endocrine neoplasia syndromes. Am J Surg 1987;154:142-8.
9. Economopoulos GC, Lewis JW Jr, Lee MW, Silverman NA. Carcinoid tumors of the thymus. Ann Thorac Surg 1990;50:58-61.
10. The BT. Thymic carcinoids in multiple endocrine neoplasia type 1. J Intern Med 1998;243:501-4.
11. Satta J, Ahonen A, Parkila S, Leinonen L, Apaja-Sarkkinen M, Lepojarvi M, *et al*. Multiple endocrine neoplastic-associated thymic neuroendocrine tumor in close relatives: Octreotide scan as a new diagnostic and follow-up modality. Two case reports. Scand Cardiovasc J 1999;33:49-53.
12. Miettinen M. Synaptophysin and neurofilament proteins as markers for neuoendicrine tumours. Arch Pathol Lab Med 1987;111:813-8.
13. Kvols LK. Therapy of the malignant carcinoid syndrome. Endocrinol Metab Clin North Am 1989;18:557-68.
14. Wang DY, Chang DB, Kuo SH, Yang PC, Lee YC, Hsu HC, *et al*. Carcinoid tumours of the thymus. Thorax 1994;49:357–60.
15. Oberg K, Hellman P, Kwekkeboom D, Jelic S. Neuroendicrine bronchial and thymic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncology 2010;21:v220-2.

How to cite this article: Gaude GS, Hattiholi V, Malur PR, Hattiholi J. Primary neuroendocrine carcinoma of the thymus. Niger Med J 2013;54:68-71.

Source of Support: Nil, **Conflict of Interest:** None declared.