An Unusual Clinical Presentation of Type - A Thymoma with Paraneoplastic Myasthenia Gravis

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Abstract: Thymus is a primary lymphoid organ composed of predominantly immature T cells which play a crucial role in the highly evolved immune system of human beings. It helps in adaptive immune responses in early life, though it undergoes gradual involution and decreases in size post puberty. Thymomas are rare neoplasms that occur in the anterior superior mediastinum in adult life. Some patients with the neuromuscular disorder such as myasthenia gravis are known to develop thymoma over a period of time. There are no known etiological factors for occurrence of thymoma in human beings. Due to the close proximity of thymus with other vital structures in the anterior mediastinum, thymectomy is a procedure associated with multiple risks revolving around surgical exploration of thymic lesions.

Presented here is a case of a 70-year-old woman who presented with a large mass in the left-side of the neck since two months; she also had history of being treated for myasthenia gravis for two years. Core biopsy was performed followed by surgical excision of the lesion which was sent for histopathological examination to the Department of Pathology of a tertiary care hospital, in Navi Mumbai, Maharashtra, India.

Keywords: Thymoma, Myasthenia gravis, T cell, Anterior mediastinum, Paraneoplastic, Thymocytes

INTRODUCTION

Thymus is an important component organ of reticuloendothelial system located in the anterior mediastinum; it is encapsulated organ which is mainly composed of epithelial cells, thymocytes and Hassall corpuscles. In most of the people, it becomes invovled and vestigial by adulthood, although it is one of sites of many pathological processes such as inflammatory, autoimmune, hyperplastic and neoplastic lesions. Neoplastic lesions of thymus are relatively less common and are categorized under the term thymomas, which constitute 1.5 cases per million every year across the globe with ostensible male preponderance [1]. Thymoma is the most common anterior mediastinal tumour which forms approximately 50 per cent of all the anterior mediastinal neoplasms [2,3]. The peak incidence of thymoma is noted to be in the 5th and 6th decades of life [4].

Among the well-known conditions associated with thymoma, Myasthenia Gravis, which is the most commonly occurring parathymic syndrome; it is found in 50 per cent of the patients diagnosed with thymoma. On the other hand, 15 per cent of people with Myasthenia gravis, an autoimmune disorder of neuromuscular junction, are incidentally diagnosed with thymoma. Thymic lymphoid hyperplasia is observed to be causing aberrant immune response in the form of myasthenia gravis in 60 per cent of the patients [5, 6].

An antigen-driven immune reaction activates inside the thymus followed by synthesis of autoantibodies that act against the acetylcholine receptor at the neuromuscular junction. Paraneoplastic myasthenia gravis is seen to arise in type A, AB and B1, B2 and B3 thymomas only [7]. Patients with myasthenia gravis express fatigue, muscle weakness and potentially fatal respiratory paralysis. The mainstay of therapy in such patients remains immunosuppression and immunomodulation.

CASE REPORT

A 70-year-old female presented with a left-sided neck swelling since 2 months, which was gradually progressing in size. The swelling was associated with pain and difficulty in deglutition. She was a known case of myasthenia gravis diagnosed two years ago, for which she was undergoing treatment.

On examination, an irregular globular swelling, 4 x 3 cm in size, was noted on the left side of the neck. The inferior border of the swelling was not palpable. Tenderness was present on palpation. There were no significant changes observed in the overlying skin.

On ultrasonography, a multilobulated hypoechoic mass measuring 5.3 x 5.3 x 4.3 cm was visualized in the left supraclavicular region inferior to the left lobe of thyroid with areas of central macrocalcification and evidence of increased internal vascularity. The findings were suggestive of malignant lesion inferior to the thyroid, probably implying Parathyroid carcinoma. On CT scan, an isodense mass measuring 5.1 x 4.8 x 4.4 cm was found to be arising from lower pole of left lobe of the thyroid gland with neovascularization as well as areas of microlcalfication. Computerized tomography findings were suggestive of a malignant mass arising from left lower part of thyroid, possibly Parathyroid carcinoma.

On evaluating the biochemical parameters, the thyroid function test revealed values within normal range in this patient with serum T3, T4 and TSH reported as 0.82 ng/dL, 5.18 ng/dl and 4.23 mIU/L, respectively. Serum PTH was 67.4 pg/mL and was found to be slightly increased. Serum calcium and serum phosphorus were within normal range with values of 9.60 mg/dl and 4.14 mg/dl, respectively.
In view of close proximity of the mass to the great vessels and other vital structures, primarily a core biopsy of the lesion was diligently performed. Seven, linear, grey-white tissue cores, the longest core measuring 1.8 cm in length and the shortest measuring 0.2 cm in length were received for histopathology.

On microscopic examination, the sections from the cores of biopsy specimen reveal sheets of plump, ovoid cells arranged in solid nests and storiform clusters, with the constituent cells showing ample pale cytoplasm and enlarged nuclei with condensed chromatin and indiscernible nucleolus (Figure 1). At places, pseudoglandular or pseudo rosette pattern is also observed (Figure 2). Few scattered lymphoid cells are also found. Focal areas show fibrous bands traversing the solid sheets of cells. No unequivocal capsular invasion is seen in the sections studied. Histomorphological features are suggestive of Thymoma – Type A according to the WHO 2015 classification [9].

Complete surgical excision of the mass was performed and sent for histopathological examination. Surgically resected specimen was encapsulated, irregularly globular, greyish-brown soft tissue mass measuring 5.4 x 5.2 x 4.5 cm along with attached fibrofatty tissue measuring 9 x 2 x 0.5 cm. Cut surface of the tumour was tan white in colour and showed lobules which were separated by seemingly fibrotic areas. Chalky white areas of calcification were also seen at the centre of the mass on cut section. Areas of haemorrhage were also seen. A single tiny lymph node measuring 0.5 cm in diameter was also found adherent to the specimen at one place.

Microscopic examination reveals a fairly circumscribed and encapsulated lesion comprising lobules of nests of pleomorphic ovoid cells, which are separated by fibrous bands. Beneath the fibrous capsule, tumour cells are arranged in solid nests and in storiform clusters with pseudo-rosette pattern in some places. Individual tumour cells are plump and ovoid in shape with enlarged nuclei showing condensed chromatin along with inconspicuous nucleoli and pale cytoplasm. Areas of necrosis with calcification are also observed at some places.
DISCUSSION

Tumours of the thymus are one among the rarest of human neoplasms. In adults, thymomas are the most common thymic tumours, which are followed by mediastinal lymphomas. In children, the mediastinum is the site of one per cent of all pediatric neoplasms. The most common mediastinal tumour incidentally happens to be non-Hodgkin lymphoma. Occurrence of thymoma during childhood is extremely unusual [10].

Many patients of thymoma can be clinically asymptomatic while few can present with symptoms pertaining to the systemic disorders associated with thymoma, such as muscle weakness, drooping eyelid, fatigue and Lambert-Eaton Myasthenic Syndrome while some patients may complain of cough, chest pain, difficulty in swallowing and dyspnoea due to local compressive effects.

The World Health Organization (WHO) Classification of thymic epithelial tumors revised in 2015 recognizes five main histologic subtypes of thymoma: Type A, AB, B1, B2, and B3 and also its other rare subtypes including micronodular thymoma with lymphoid stroma (MNT) [8, 9]. Type C is classified as thymic carcinoma and has a highly malignant clinical course. Type A and type AB have a comparatively good prognostic outcome. However, atypical type A thymoma is among the aggressive types of thymoma [16].

Conventional morphologic patterns are observed in most of the thymomas on histopathological examination; nevertheless, a few rare variants with uncommon features such as microscopic thymoma, thymolipoma, thymofibrolipoma, lipofibroadenoma and sclerosing thymoma have also been cited in literature. [11, 12, 13]

In case of Type A thymomas, few genetic alterations have been identified with 6p deletion being a recurrent alteration [18]. The mutations identified in other types of thymomas include p53, KIT, Cyclin-dependent kinase inhibitor 2A (In Types B3 and C). Rarely mutations are seen to occur in n-ras, k-ras, cyclin D1, SMARCB1, ERBB4, FGFR3, and STK11 genes [17].

Thymomas are associated with multiple paraneoplastic, autoimmune and systemic disorders, such as myasthenia gravis, collagen-vascular disease, systemic lupus erythematosus, Cushing’s syndrome, hypogammaglobulinemia, pure red cell aplasia and syndrome of inappropriate antidiuretic hormone secretion [14, 15].

Clinical diagnosis of thymoma depends on clinical features arising out of local and systemic effects of thymic mass in the mediastinum and also features of paraneoplastic syndromes. Paraneoplastic syndromes arouse suspicion of existence thymoma which is generally diagnosed by various imaging studies with CT (Computed tomography), presently, being the first investigation

Figure 5: Photomicrograph showing thymic lobules separated by fibrous bands (H and E, 4x).

Figure 6: Photomicrograph shows encapsulated lesion with nests of tumour cells (H and E, 10x).

Figure 7: Photomicrograph shows oval to spindle shaped cells arranged in pseudorosettes with bland nuclei, dispersed chromatin and inconspicuous nucleoli (H and E, 40x).

Figure 8: Photomicrograph depicts tumour cells forming focal storiform pattern (H and E, 40x).
of choice to analyze any mediastinal growth and to assess its spread to the adjacent structures and to distant organs in cases of malignancy [16].

On electron microscopy, thymoma cells appear to have numerous inter-digitating elongated cell processes linked together with desmosomes. Intracytoplasmic tonofilaments are mostly conspicuous. On Immunohistochemistry, the epithelial component of thymoma stains for cytokeratin (CK5/6 and CK7) and the epithelial membrane antigen (EMA). It has been observed that the glandular structures demonstrate stronger staining for cytokeratin as compared to the spindled tumour cells in type A thymoma. The neoplastic epithelial cells may also stain with certain B cell markers, such as CD20 in cases of type A thymoma. The lymphoid component is predominantly composed of thymocytes which are positive for TdT, CD 1a, CD3 and CD 99a [4].

The differential diagnosis for an anterior mediastinal mass includes invasive thymoma, thymic carcinoma, neuroendocrine tumours, and various types of lymphoma, primary sarcomatous tumours, malignant germ cell tumours and metastatic tumours.

CONCLUSION

Thymomas and thymic carcinomas are rare anterior mediastinal tumours with an indolent growth pattern. However, they could invade locally or metastasise regionally and are often associated with a number of immune- and non-immune-mediated paraneoplastic syndromes. In the present case, the tumour had an unusual presentation and growth pattern which was clinically thought to be a neoplastic lesion arising from the lower portion of left lobe of thyroid, specifically from the left parathyroid gland, infiltrating and invading various neck and mediastinal structures with extensive areas of adhesions, apart from ending as growth in the left supraclavicular region. This makes it an unusual and intriguing neoplasm of thymus which had extended by contiguity beyond anterior mediastinum.

The most effective treatment for thymomas remains complete surgical removal of the tumour. Adjuvant radiotherapy is recommended in certain cases of invasive thymoma. Thymectomy is advised in all cases of thymoma irrespective of the stage of myasthenia gravis. Possibility of recurrence in case of type A thymomas is very rare.

REFERENCES AND BIBLIOGRAPHY