

Case Report

Rapid development of thymic neuroendocrine carcinoma despite transcervical thymectomy in a patient with multiple endocrine neoplasia type 1

Dhalapathy Sadacharan, Sagili Vijaya Bhaskar Reddy¹, Vinita Agrawal², Gaurav Agarwal

Department of Endocrine and Breast Surgery, ¹Endocrinology and ²Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

ABSTRACT

Thymic neuroendocrine (NE) tumors are a rare manifestation of multiple endocrine neoplasia syndrome type 1 (MEN-1). They are malignant and aggressive tumors and form a major cause of mortality in MEN-1. Transcervical thymectomy (TCT) at the time of parathyroid surgery for primary hyperparathyroidism (PHPT) in MEN-1 usually prevents thymic NE tumors. We report a 56-year-old nonsmoker male with sporadic MEN-1 who presented with thymic NE carcinoma developing rapidly within a span of 8 months after subtotal parathyroidectomy and TCT for PHPT. We present a brief review of literature on this rare NE malignancy, focusing on its occurrence despite TCT. This case highlights the fact that thymic NE carcinoma may develop even after TCT in MEN-1. Regular surveillance for these aggressive thymic NE tumors is mandatory even after TCT in MEN-1 setting.

Key words: Multiple endocrine neoplasia type 1, thymic neuroendocrine carcinoma, transcervical thymectomy

INTRODUCTION

Thymic neuroendocrine (NE) tumors associated with multiple endocrine neoplasia type 1 (MEN-1) are rare, variably documented in 1-8% cases.^[1-4] Thymic NE tumors are usually detected about 7-29 years following surgical treatment of primary hyperparathyroidism (PHPT) in MEN-1.^[3] Transcervical thymectomy (TCT) at the time of parathyroid surgery for PHPT usually prevents thymic NE tumors.^[1] The occurrence of thymic NE tumors is very rare after TCT as part of the parathyroidectomy procedure for PHPT. Here we report a case of thymic NE carcinoma developing within a span of 8 months

after subtotal parathyroidectomy and TCT for PHPT in a MEN-1 patient.

CASE REPORT

A 56-year-old non-smoker male presented with generalized bodyaches, low back pain, and proximal myopathy of 1-year duration without any fragility fractures. Examination revealed bony tenderness over the sternum and proximal muscle weakness of the lower limbs. Laboratory evaluation revealed hypercalcemia (serum total calcium 12.8 mg/dl, normal 8.5-10.5 mg/dl), hypophosphatemia (serum phosphorus 2.1 mg/dl, normal 2.5-4.5 mg/dl), normal serum albumin (3.8 g/dl), normal serum alkaline phosphatase (136 IU/L, normal 50-150 IU/L), vitamin D sufficiency (serum 25OH vitamin D 31 ng/ml), and normal renal function (serum creatinine 1.2 mg/dl). Hypercalcemia was PTH dependent (serum calcium 12.8 mg/dl with high serum intact PTH 215 pg/ml, normal 15-70 pg/ml). His hemogram and ESR were unremarkable (Hb 13.4 g/dl, TLC 6700/mm³, platelet count 2.8 lakhs/mm³, and peripheral smear showed

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Corresponding Author: Dr. Gaurav Agarwal, MS, DNB, PDC (Endocrine Surgery), Cert RACS (Australia), FACS, Professor, Department of Endocrine and Breast Surgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow - 226 014, Uttar Pradesh, India.
E-mail: gaurav@sgpgi.ac.in

normocytic, normochromic RBCs, ESR 20 mm at end of the first hour). A diagnosis of sporadic PHPT was made. Bone mineral density by dual energy X-ray absorptiometry showed osteoporosis (T-score -2.7 at lumbar spine, -2.0 at total hip, and -3.4 at distal forearm). Ultrasound neck revealed multiglandular parathyroid enlargement, while a ^{99m}Tc tetrofosmin parathyroid scan showed a right inferior parathyroid tumor. The patient was advised surgery as he had serum calcium >12 mg/dl and osteoporosis. The patient was subjected to bilateral neck exploration, where asymmetrical parathyroid hyperplasia was found. Subtotal parathyroidectomy (3.5 gland) with TCT was performed. TCT was performed to identify any supernumerary parathyroid glands. No supernumerary parathyroid glands were identified, and the excised thymus was unremarkable. The patient had an uneventful postoperative recovery. Histopathology showed multiglandular parathyroid hyperplasia and a normal thymus.

On follow-up, 8 months after parathyroidectomy, he presented with heaviness in the left side of the chest, dry cough, and exertional dyspnea of 3 months duration. Chest radiograph revealed mediastinal widening with an oval well-circumscribed homogenous opacity (Figure 1b-dark arrow) in left hemi-thorax. Contrast-enhanced computed tomography (CT) of thorax showed a 10×6.7 cm inhomogeneously enhancing anterior mediastinal soft tissue mass in the prevascular space on the left side, in close proximity to the ascending aorta and arch of aorta [Figure 2]. Chest radiograph done 9 months earlier [Figure 1a] did not show any mediastinal widening.

^{99m}Tc Methylene diphosphonate (MDP) whole-body skeletal scan showed increased tracer uptake at thoraco-lumbar vertebrae and multiple ribs suggestive of skeletal metastases. A CT-guided biopsy from D11 and L3 vertebrae showed metastatic NE carcinoma.

The anterior mediastinal mass was excised *in toto* via trans-sternal approach. On surgery, the tumor was not found to invade any of the adjacent structures. The excised tumor measured $12 \times 7 \times 5$ cm and weighed 264 g [Figure 3]. On microscopy [Figure 4a and b], the tumor was partially encapsulated, and was composed of rosettes of tumor cells traversed by thin fibro-vascular septae. The tumor cells displayed round to oval nuclei, granular chromatin, occasional nucleoli, and moderate amount of granular to pale cytoplasm with areas of punctate necrosis and lympho-vascular emboli suggestive of thymic NE carcinoma. Immuno-histochemical studies were suggestive of positive staining for chromogranin and synaptophysin, but absence of staining for NSE and vimentin [Figure 4c and d], consistent with thymic NE carcinoma.

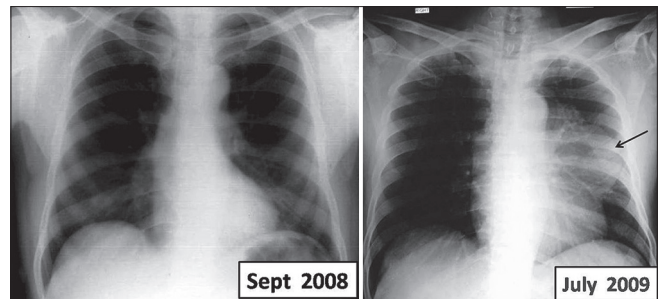


Figure 1: Chest radiographs done 9 months apart – radio-opacity in the left hemi-thorax in July 2009 radiograph (marked with arrow) was not present in September 2008 radiograph

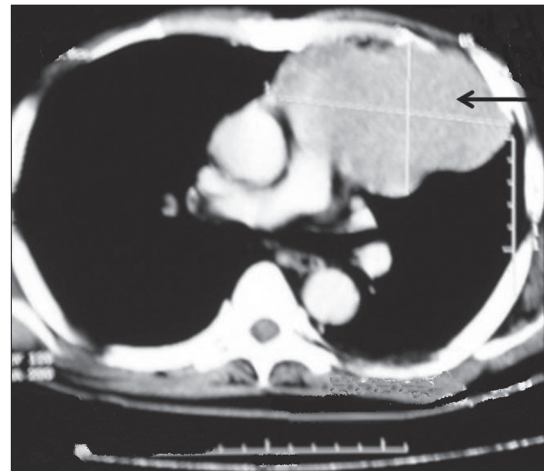


Figure 2: Contrast-enhanced computed tomogram of the thorax showing large solid anterior mediastinal mass (marked with arrow) to the left of mid-line



Figure 3: Lobulated solid tumor which was homogenous grayish white and fleshy on the cut surface

With strong suspicion of sporadic MEN-1, in view of coexistence of PHPT with metastatic thymic NE carcinoma, work up for MEN-1 was done, which revealed raised fasting serum gastrin (18,000 pg/ml, normal <200) suggestive of gastrinoma. His serum prolactin (12 ng/ml, normal 2.1-17.7 ng/ml) and serum IGF-1 (131 ng/ml) were within normal range, thereby ruling out any functioning

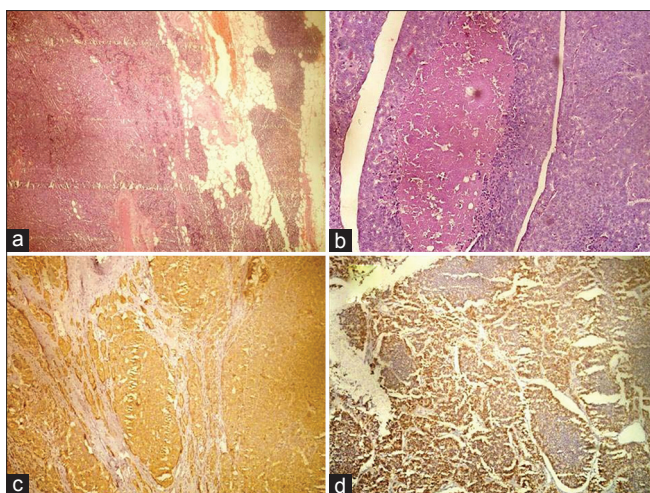


Figure 4: Histopathology and immuno-histochemistry. (a) Tumor with adjacent thymus, H and E, $\times 100$. (b) tumor cells displaying rosette formation and necrosis, H and E, $\times 400$. (c) chromogranin immunopositivity, $\times 200$. (d) cytokeratin immuno-positivity $\times 200$

pituitary tumors. There was no family history of disorders suggestive of MEN-1 (family pedigree chart, Figure 5). Biochemical screening of family members for MEN-1 was also negative. Somatostatin-receptor scintigraphy with ^{68}Ga -DOTANOC PET/CT revealed somatostatin receptor expressing tumors involving second part of duodenum, head, body, and tail of pancreas, suggestive of gastrinomas. There was no evidence of somatostatin receptor expression in the mediastinum or vertebrae, suggesting that the vertebral metastases were from the thymic NE carcinoma and not from the gastrinomas.

The diagnosis of sporadic MEN-1, with two major endocrine gland involvement (PHPT due to parathyroid hyperplasia and gastrinomas) along with a rare occurrence of thymic NE carcinoma was apparent. The thymic NE carcinoma had evolved rapidly within a span of 8 months after parathyroidectomy and TCT, and presented with bony metastases. With wide-spread metastatic disease, the patient was managed palliatively (pantoprazole, zoledronic acid 4 mg intravenous infusion 4 weekly and Lanreotide 20 mg intramuscular 4 weekly). The patient has been followed up with serum alkaline phosphatase, calcium, chromogranin and gastrin estimations; and ^{68}Ga -DOTANOC PET/CT and $^{99\text{m}}\text{Tc}$ MDP bone scans at 6 monthly intervals, and other appropriate imaging such as abdominal and thoracic CE-CT scans. He has been treated with external beam radiotherapy as well as ^{153}Sm Samarium therapy for palliation of painful spinal lesions. Thirty months in follow-up, biological therapy in form of Tab. Sunitinib maleate- a multi-target tyrosine kinase inhibitor- 37.5 mg per orally, once daily was initiated in view of progressive metastatic disease, including liver, lungs and skeletal metastases, which he has received for 18 months with effective symptom palliation,

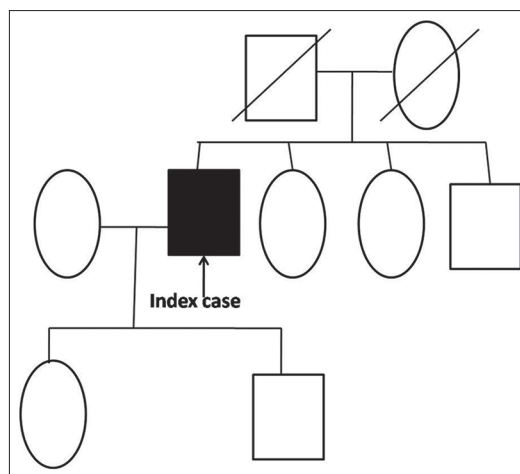


Figure 5: Family pedigree chart showing index case of MEN-1 and unaffected family members

and manageable toxicity. He suffered osteo-necrosis of the jaw- a known complication of long-term zoledronic acid usage, which has been managed by discontinuation of Inj Zoledronic acid and other supportive care. Four years since being operated upon for the thymic N-E carcinoma, the patient is alive, ambulatory, is reasonably symptom free with good quality of life, and is normocalcemic, with no loco-regional recurrence of the thymic tumor.

DISCUSSION

Thymic NE tumors have been variably reported in MEN-1 from 1% to 8% of cases.^[1-4] In recent studies, thymic NE carcinoma has emerged as a major cause of mortality in MEN-1 along with gastro-entero pancreatic tumors.^[1,5] Thymic NE tumors in MEN-1 are commoner in males and smokers and are almost always hormonally inactive and diagnosed incidentally.^[3,4,6] They are malignant, aggressive tumors and are widely invasive and metastatic at presentation (usually to bone).^[3,4,6] Thymic NE tumors are never the presenting feature of MEN-1 and almost always occur after PHPT, providing an opportunity for prophylaxis for these tumors with TCT at the time of parathyroid surgery.^[1,3,4]

While operating a PHPT patient with multigland parathyroid disease, routine TCT is usually performed to take care of the supernumerary parathyroid glands that can be found within the thymus gland in 15-20% patients.^[1,7] The utility of TCT in preventing the thymic NE tumors in MEN-1 patients is a matter of debate.^[7] Our patient developed thymic NE carcinoma despite TCT being performed as part of his first operation (sub-total parathyroidectomy). TCT could not prevent thymic NE carcinoma in our patient, as also reported by others.^[3,8] This may be because TCT results in removal of only

40-50% of thymic tissue. In our patient, the thymic NE tumor was arising from thymic limb low down in the left pulmonary hilar region, which could not have been removed by TCT. Regular surveillance for thymic NE tumors even after TCT in MEN-1 patients is mandatory.^[3] More radical thymectomy procedures like the trans-sternal thymectomy or video-assisted thoracoscopic surgical thymectomy have not been reported as a prophylactic procedure in MEN-1 patients.

Usually, PHPT is the first component of MEN-1 manifesting in the third to fourth decade.^[1,2] Thymic NE tumors present later, usually 15-20 years after PHPT.^[3] In contrast, our patient had a rapid presentation of thymic NE carcinoma, which was not evident on the chest radiograph done about 9 months earlier during management of PHPT. Thymic NE carcinomas are known to have rapid progression and metastatic course.^[3,4,6] The rapid pace of development of thymic NE carcinoma with bone metastases in our patient underscores its aggressiveness and metastatic potential. Current guidelines for surveillance of MEN-1 recommend screening for thymic NE tumors once every 1 to 2 years with CT or MRI of thorax,^[1] although currently annual screening is advised by newer studies.^[3] As MEN-1 patients undergo parathyroid surgery almost universally, TCT is recommended for prevention of thymic NE tumors.^[1]

A complete surgical excision through a trans-sternal route is the only curative treatment for thymic NE tumors. Aggressive enbloc resection of involved structures is recommended.^[9] Some authors have advocated routine postoperative radiotherapy to prevent loco-regional recurrence.^[3] Our patient did not have any direct invasion of adjacent structures inspite of its large size and the histological margins were reported uninfiltated. In view of the multiple bone metastases, postoperative radiotherapy seemed futile.

CONCLUSION

We report a sporadic MEN-1 patient cured of PHPT, presenting with gastrinoma and aggressive metastatic

thymic NE tumor that developed within a year after subtotal parathyroidectomy along with TCT. MEN-1 patients need to be screened for thymic NE tumors by routine annual CT or MRI of the thorax even after TCT at the time of parathyroid surgery. TCT may be ineffective in preventing subsequent development of thymic NE tumors.

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