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Thymic neuroendocrine tumour (carcinoid): clinicopathological features of four patients with different presentation

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Abstract

Thymic carcinoids are aggressive and present at an advanced stage. This article describes the utility of ^{68}Gallium-1,4,7,10-traazacyclododecane-NI, NII, NIII, NIIII-tetra acetic acid-(D) – Phel1-Tyr3-octreotide positron emission tomography (^{68}Ga DOTATOC PET-CT-scan) and clinicopathological features of four thymic carcinoid tumours. Two typical, one atypical, and one large cell neuroendocrine carcinoma (LCNEC) were analysed. There were three males and one female with a mean age of 33 years. Three patients had a stage III and one had a stage II tumour. Preoperative ^{68}Ga DOTATOC PET-CT-scan of three patients did not show uptake of radiotracer in the tumour. Three patients were disease free at 19–27 months follow-up. The patient with LCNEC developed recurrence in the lumbar vertebrae. There is no locoregional recurrence of tumour in any of our patients. Complete surgical resection of the tumour with invaded adjacent structures, postoperative radiotherapy to the tumour bed helps in obtaining disease free survival.
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Keywords: Neuroendocrine tumour; Thymic carcinoid; Cushing's syndrome; ^{68}Ga DOTATOC PET-CT

1. Introduction

The thymic neuroendocrine tumours are epithelial tumours of thymus gland that are predominantly or exclusively composed of neuroendocrine cells which can be demonstrated on immunohistochemistry. The neuroendocrine tumours of the thymus comprise of typical carcinoid (TC) and atypical carcinoid (AC), as well as large cell carcinoma (LCC) and small cell carcinoma (SCC). These tumours are uncommon and occur in all age groups with male predominance.

2. Patients and methods

All the thymic tumours operated in a single surgical unit at our hospital were analysed retrospectively. A total of 142 thymic tumours were operated since 1997. Thymic neuroendocrine tumours were detected in four patients (2.8%) in the final histopathology report. None of the four patients showed evidence of myasthenia gravis. The data were collected from the operative notes, patient clinical case file, follow-up register of the surgical unit, and histopathology reports. Role of ^{68}Gallium-1,4,7,10-tetraazacyclododecane-NI, NII, NIII, NIIII-tetra acetic acid-(D) – Phel1-Tyr3-octreotide positron emission tomography (^{68}Ga DOTATOC PET-CT-scan) in detecting thymic carcinoid was observed. The clinical information regarding the patient was updated by telephone conversation with the patient.

The histopathology slides of all the four patients were re-examined by a team of pathologists well-versed with the thymic pathology. Immunohistochemistry of the slides with neuroendocrine markers chromogranin A, synaptophysin, neuron specific enolase (NSE) were reviewed. Ultra structural study of the tumour tissue using electron microscope (EM) was carried out in one patient with large cell neuroendocrine carcinoma (LCNEC). The histopathological features examined under light microscopy are architectural pattern, areas of necrosis, and mitotic activity. The tumours were graded into TC, AC, SCC, and LCNEC, according to the World Health Organization criteria for thymic neuroendocrine tumours. Clinical postsurgical staging of Masaoka for thymoma was used to describe the stage of the four thymic carcinoid tumours.

3. Results

The clinical presentation and survival outcome of the four patients are described in Table 1. There were three males and one female with a mean age of 33 years. Case 1 had an asymptomatic tumour which was detected on routine chest X-ray. Contrast enhanced computed tomography (CECT) of the chest revealed a thymic tumour of

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Table 1. Presentation, treatment, and follow-up

Case no.	Age (years)	Sex	Presentation	Syndrome	Surgery	Tumour size (cm)	Adjuvant therapy	Recurrence (months)	Survival status (months)
1	39	M	Asymptomatic	Nil	R0 resection	12×10×7	RT	Nil	19
2	26	M	Obesity, hypertension, diabetes, hypothyroidism, proximal myopathy, psychiatric features	Cushing's syndrome	R0 resection	5×3×3	RT	Nil	27
3	23	F	Obesity, hypertension, proximal myopathy, psychiatric features, hirsutisim, skin pigmentation	Cushing's syndrome	R0 resection	1.2×1×0.3	RT	Nil	26
4	44	M	Chest pain, dyspnoea	Nil	R0 resection	14.5×11×6	RT+octreotide therapy	Recurrence at lumbar vertebrae	13

RT, radiotherapy.

11.7×9.9 cm size with calcification and central necrosis. ^{18}F-fluorodeoxy glucose (^{18}F-FDG) PET-CT showed intense tracer uptake with standardized uptake value (SUVmax) of 6.5. Computed tomography (CT) guided tru-cut biopsy of the mass was reported as thymic neuroendocrine carcinoma. Case 2 and 3 had Cushing's syndrome due to ectopic adrenocorticotrophic hormone (ACTH) secretion. Internal jugular vein sample to peripheral ACTH (IJVS: P-ACTH) ratio <2.0 in the basal state pointed towards a peripheral source of ACTH production (Table 2). CECT chest revealed a thymic tumour. Magnetic resonance imaging (MRI) of the brain with i.v. gadolinium showed normal MR signal intensity in the pituitary gland. CECT and MRI abdomen scans showed normal adrenal gland. Case 4 presented with pain over the sternum and dyspnoea. CECT chest and abdomen showed an anterior mediastinal mass of 8×7 cm with invasion of upper two-third of the sternum without any evidence of distant metastasis. Radionuclide bone scan revealed increased tracer concentration in upper two-third rd of the sternum without any other focus of abnormal radiotracer uptake.

The role of ^{68}Ga DOTATOC PET-CT-scan was studied in three patients who had thymic tumour with preoperative histology suggestive of carcinoid (case 1) or tumour suspicious of secreting ectopic ACTH (case 2 and 3). None of these tumours showed any uptake of radiotracer (Fig. 1). Case 4 had preoperative CT guided fine needle aspirate suggestive of poorly differentiated carcinoma and ^{68}Ga DOTATOC PET-CT-scan was not done for him.

Three patients had Masaoka stage III and one had Masaoka stage II tumour. Case 1 had the tumour adherent to the pericardium (stage III). The tumour was resected en bloc with the underlying pericardium along with mediastinal lymph nodes. Case 2 had thymic carcinoid with invasion of the pericardium and the left brachiocephalic vein (stage III). The tumour was resected with underlying pericardium and left brachiocephalic vein. The left brachiocephalic vein was reconstructed with a vascular graft. Case 3 had a small tumour without gross features of invasion and video-assisted thoracoscopic resection was performed. Histopathological examination reported invasion of surrounding fatty tissue with positive resection margin for tumour cells (stage II). Hence, re-exploration through median sternotomy and excision of pericardium in the tumour bed, mediastinal lymph nodes, and pericardial fat was performed. She developed thrombosis of left pulmonary artery after the second surgery. It was managed conservatively with anticoagulant therapy and follow-up CT angiography confirmed resolution of thrombus and patency of the left main pulmonary artery. Case 4 had a tumour with invasion of upper two-thirds of the sternum (stage III). En-bloc resection of the tumour with pericardium, upper two-thirds of the sternum with bilateral medial ends of clavicle and upper five costal cartilages, and a mediastinal lymphadenectomy was performed. Chest wall was reconstructed with polypropylene mesh covered by bilateral pectoralis major muscle advancement flap.

All the tumours showed features of neuroendocrine differentiation (Table 3). There were two TC (Fig. 2a–d) and one LCNEC (Fig. 2e,f). Case 3 (AC) showed extensive areas of necrosis. All the tumours showed positive staining with neuroendocrine markers like chromogranin A, synaptophysin. Case 2 and 4 showed positive staining with NSE and case 4 showed positive staining for CD117. EM to study for ultra structural features showed dense core granules in case 4.

Table 2. Hormone profile of ACTH dependent Cushing's syndrome

Case no.	Cortisol morning (μg/dl)	Cortisol evening (μg/dl)	Cortisol LDDST (μg/dl)	Cortisol HDDST (μg/dl)	ACTH R-IJV (pg/dl)	ACTH L-IJV (pg/dl)	ACTH periphery (pg/dl)	Prolactin central/peripheral	IJVS: P-ACTH ratio
2	42.10	37.24	58.56	63.44	80.22	84.85	57.39	13.25/10.14	1.47
3	36.62	27.21	33.84	30.77	50.55	70.37	59.16	15.40/14.73	1.18

ACTH, adrenocorticotrophic hormone; IJVS: P-ACTH, internal jugular vein sample to peripheral-ACTH; LDDST, low-dose dexamethasone suppression test; HDDST, high-dose dexamethasone suppression test; IJV, internal jugular vein.

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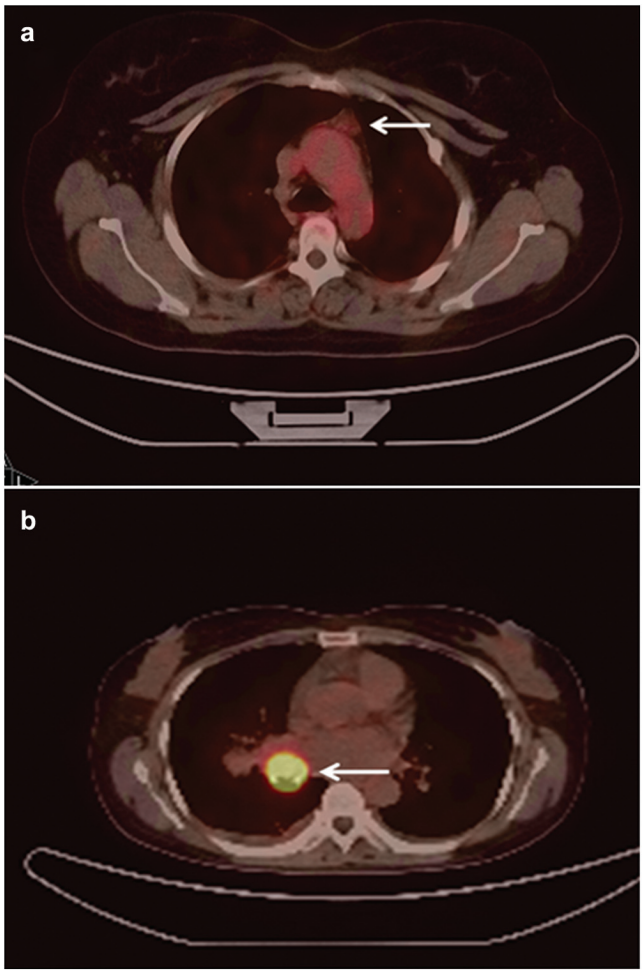

Fig. 1. ^{68}Ga DOTATOC PET-CT-scans (a) showing no uptake of radiotracer in thymic carcinoid (arrow) and (b) showing intense uptake of the radiotracer in bronchial carcinoid (arrow) for comparison. ^{68}Ga DOTATOC PET-CT, ^{68}Gallium-1,4,7,10-tetraazacyclododecane-NI, NII, NIII, NIIII-tetra acetic acid-(D) – Phel1-Tyr3-octreotide positron emission tomography.

All the four patients are alive and healthy except case 4 who has been diagnosed with a recurrent disease of the lumbar vertebrae. Case 1 is doing well in follow-up at 19 months without evidence of locoregional and distant metastases. Case 2 had complete resolution of psychiatric features. His blood sugar, blood pressure, and thyroid hormone profile normalized within a period of six weeks. He has lost his extra body weight (body mass index, BMI 46 → BMI 25) and doing well at 27 months follow-up. Case 3 recovered well and her body weight reduced (BMI 39 → BMI 24) with complete resolution of psychiatric features. Her blood pressure normalized, hirsutism disappeared, and pigmentation of skin is gradually decreasing. Case 4 developed intense pain over the lumbar vertebrae with paraplegia at seven months postoperatively. Bone scan detected metastasis to the lumbar vertebrae without evidence of locoregional recurrence on CECT chest. He was given radiotherapy (RT) to the affected vertebrae as he was not willing to undergo surgical decompression of his spinal cord.

4. Discussion

These tumours are uncommon and occur in all age groups with a male predominance. Rosai et al. first described thymic carcinoid tumours as a distinct clinical entity and their association with Cushing's syndrome and multiple endocrine neoplasia (MEN) [1]. About 25% of patients with thymic carcinoid present with Cushing's syndrome due to ectopic ACTH production. An association with MEN type 1 syndrome is seen in approximately 15% [2]. The majority of the reported cases were asymptomatic and were detected incidentally on routine roentgenograms. They can also present with symptoms of local compressive effect on neighbouring structures. Approximately 80% cases of endogenous ACTH-dependent Cushing's syndrome are caused by a pituitary corticotrophic adenoma and the rest are caused by an extra pituitary tumour (ectopic ACTH syndrome) or very rarely by an ectopic corticotropin-releasing hormone secreting tumour. The clinical presentation resembles many of the phenotypic features of modern life: obesity, hypertension, and depression [3].

The occult ectopic ACTH syndrome reflects the presence of hypercortisolism due to a non-pituitary, ACTH-secreting neoplasm. The majority of occult ectopic ACTH-secreting neoplasms are either bronchial or thymic carcinoids or other neuroendocrine tumours (e.g. islet cell, medullary carcinoma of the thyroid or pheochromocytoma) [4]. CECT

Table 3. Histological and immunohistochemical features

Case no.	Architecture	Mitotic rate	Necrosis	CD117	Chromogranin A	Synaptophysin	NSE	Histology WHO type	EM
1	Cells in ribbon and festoon formation	<2/10 hpf	Absent		+	+	–	Typical carcinoid	Not done
2	Polygonal cells in cords and trabeculae with moderate to abundant cytoplasm	<2/10 hpf	Absent		+	+	+	Typical carcinoid	Not done
3	Plasmacytoid tumour cells arranged in sheets with focal acinar pattern	2–8/10 hpf	Focal		+	+	–	Atypical carcinoid	Not done
4	Large tumour cells with prominent nucleoli and brisk mitotic activity	>10/10 hpf	Focal	CD117+	+	+	+	Large cell neuroendocrine carcinoma	Dense core neurosecretory granule

NSE, neurone specific enolase; EM, electron microscopy; WHO, World Health Organization; hpf, high power field.

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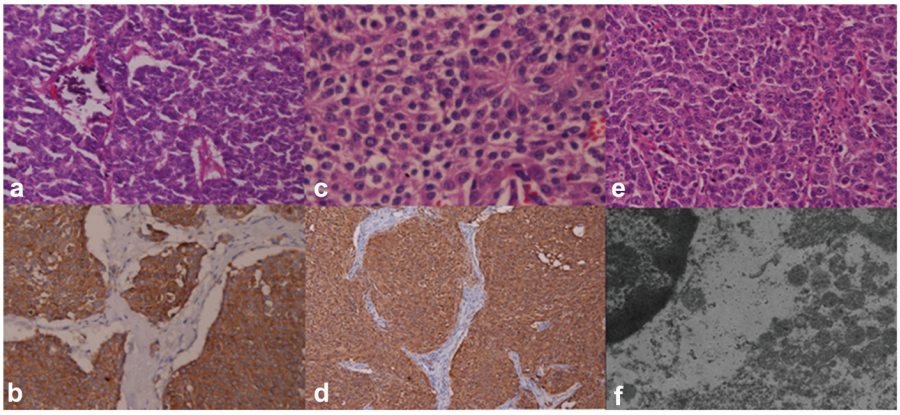

Fig. 2. Microphotographs (a) typical carcinoid in case 1 showing cords and trabeculae separated by delicate capillaries with focal calcification (H&E ×200). (b) Synaptophysin positivity in tumour (IHC ×200). (c) Typical carcinoid in case 2 showing plasmacytoid tumour cells arranged in sheets with focal acinar pattern (H&E ×400). (d) Chromogranin positivity in the tumour (IHC ×200). (e) Large cell neuroendocrine carcinoma showing prominent nucleoli and brisk mitotic activity (H&E ×200). (f) Electron microscopy showing presence of dense core neurosecretory granules.

of chest and abdomen has the highest detection rate when looking for an occult ACTH-secreting neoplasm. Biochemical diagnosis of Cushing's syndrome can be done by internal jugular vein (IJV) sampling which is less invasive than petrosal sinus sampling. IJV sampling correctly identifies ACTH-secreting pituitary adenomas in 80% of patients with proven Cushing disease [5].

Ectopic ACTH secreting tumours can be exceedingly small and may not be detected on CT chest or abdomen scans. Carcinoid tumours have been shown to express somatostatin receptors (SSRs) and thus can be highlighted with the radiolabelled somatostatin analogue octreotide in more than 80% of cases [6]. However, for thymic carcinoid, the literature has conflicting reports. Leondi et al. in a review of 28 patients of thymic carcinoid, found all but one patient to have a positive scan with SSR scintigraphy [7]. Whereas, a study of SSR expression in resected thymic carcinoid specimens by Tiffet et al. revealed none of the 12 cases to be positive for SSRs [8]. Thus, while the presence of SSRs on the surface of carcinoid tumours in general is well-accepted and SSR scintigraphy is useful in them, their status in carcinoid of thymus is unclear. Low spatial resolution of SSR scintigraphy is another problem. This problem has been addressed by the use of DOTATOC, a SSR analogue which can be combined with a PET-CT to give high spatial resolution [9]. There is only one report in the literature in which metastatic thymic carcinoid tumours were evaluated by DOTATOC scan and found to be positive [10]. To the best of our knowledge, this is the first time that ^{68}GA DOTATOC PET-CT has been used to evaluate a non-metastatic functional thymic carcinoid. Unlike pulmonary and abdominal carcinoid, it did not prove to be useful in our patients. It was possibly due to low or absent expression of SSRs on the surface of thymic carcinoid tumours. However, this issue needs evaluation in larger number of patients to determine the exact role of ^{68}Ga DOTATOC PET-CT-scan in thymic carcinoid.

Thymic carcinoids often behave aggressively with advanced disease due to the invasion of adjacent mediastinal structures, local recurrence, or metastases. An aggressive surgical approach in the management of thymic neuroendocrine tumour offers the best possible treatment for this aggressive disease due to lack of effective chemotherapy and RT. The prognosis is poor in the setting of partial or incomplete surgical resection [11, 12]. All our patients presented with tumours at an advanced stage with invasion of adjacent structures. We could successfully complete a resection of the tumour with adjacent involved structures in all our patients.

The role of chemotherapy and RT in the postoperative management of thymic neuroendocrine tumour continues to be debated due to the paucity of cases reported. Adjuvant therapy may offer local disease control, it is not effective in eradicating tumours, nor does it prevent the development of recurrence or metastases [12]. Single agents or combination drug therapies with 5-fluorouracil, streptozocin, carmustine, VP-16, cisplatin have been used previously without any significant impact on the recurrence rate or overall survival [2, 11]. Thymic carcinoid tumours express SSRs and there are successful interventions with long acting octreotide in primary and metastatic tumours [13, 14]. Case 4 with LCNEC was also given adjuvant long-acting octreotide therapy. All of the four patients were given adjuvant RT to the mediastinum to prevent local recurrence. All the four cases received total field radiation of 40 Gy (2 Gy fractions, 5 fractions per week over four weeks). None of the patient has loco-regional recurrence on follow-up CECT chest scan. One of the patients with LCNEC did develop recurrence in the lumbar vertebrae in spite of multimodality therapy.

5. Conclusion

Thymic neuroendocrine tumours are aggressive neoplasm and often present with invasion of the adjacent structures. Surgical excision of the tumour provides the best chance of survival and resolution of the manifestations of carcinoid producing Cushing's syndrome. Single institution experience of large case series is rare and hence, treatment modality of this rare neoplasm is devised on the basis of experience of the published cases in the literature. Radical surgery with resection of all involved adjacent structures and adjuvant local RT will provide good local disease control.

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Distant metastasis, however, will continue to be an issue and awaits a better systemic form of therapy.

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