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CASE REPORT

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A case of madness resulting in a fortunate outcome; case report of a psychotic break as a result of cortisol secreting thymic neuroendocrine thymic tumor

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ABSTRACT

Representing a mere 2–5% of the total thymic malignancies and 0.4% of total carcinoid tumors, primary thymic neuroendocrine tumors (NETs) are the zebras of the thymic neoplasms. They were initially characterized as 'epithelial thymomas'; later, the term carcinoid tumors was coined by Rosai and Higa. These tumors are highly unpredictable in their presentation and prognosis. Coupled with variable clinical presentation, rare pathologic diagnosis and absence of diagnostic and prognostic parameters, it is a challenge for both patients and clinicians. Treatment entails local definitive therapy, symptom control and systemic chemoradiation given either pre or post operatively based on staging and resectability. We hereby report a peculiar case of psychosis that likely resulted from one such rare tumor.

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1. Introduction

As the least common of the Thymus neoplasms, their incidence is approximately 0.2 per million in the USA. Thymic neuroendocrine tumors (NETs) are predominantly seen in males, with a 3:1 distribution at a median age of 57 years. The largest case series was over a period of 33 years with only 160 patients reported to the Surveillance, Epidemiology and End Results database. An association with multiple neuroendocrine neoplasia type 1 (MEN1) [1–3, 4–9] has been observed, with 25% of the NETs occurring in patients with the syndrome. Most of the identified cases were heavy smokers, though a clear association has not been established. Thymic NETs represent a malignant potential that is more substantial than other MEN1-associated tumors.

In 2015, World Health Organization (WHO) classified thymic neoplasm and among them the primary NETs as in Table 1.

Diagnosis of thymic NETs is histological and based on the presence of neuroendocrine features. The disease is classified as: (1) well differentiated (58%), (2) moderately differentiated (10%) and (3) poorly differentiated (12%). Given its location, the range of differentials is wide and correct histologic diagnosis remains crucial to guide treatment and prognosis.

Thymic NETs can also rarely be seen in the middle or posterior compartment. Typically, at diagnosis they are locally invasive and in addition about 50% have lymph node involvement [10].

Most patient present with local mass effects, such as SVC syndrome, cough, dyspnea and chest pain. Half of the diagnosed patients have endocrinopathies, most common of which is Cushing's syndrome. This is secondary to the ectopic adrenocorticotropic hormone production [11,12]. Other endocrinopathies include hyperparathyroidism [13]. The paraneoplastic conditions associated are polyarthropathy, proximal myopathy, peripheral neuropathy, hypertrophic osteoarthopathy and lambert-Eaton syndrome and rarely acromegaly and Syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced hyponatremia.

Laboratory testing might generally be of not much help, since half of the thymic NETs do not produce hormones. Chromogranin A may be increased but is a nonspecific finding. Goals of initial evaluation are characterization of the size, the extent of encroachment and need for biopsy. A multiphasic CT scan may be sufficient as a first step. Large masses require a surgical biopsy with en bloc resection of the adjacent tissue. However, for smaller ones a complete thymomectomy is recommended. Once the diagnosis of thymic NET is established, cross-sectional imaging with either indium-111 pentrtreotide (OctreoScan) or, if available, Gallium Ga-68 DOTATE integrated positron emission tomography/CT (Somatostatin receptor-based diagnostic imaging) is advised. The superiority of these imaging modalities is in

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Table 1. WHO classification for thymic neoplasms.

Thymic neuroendocrine tumors	
Typical carcinoid tumors	Low grade
Atypical carcinoid tumors	Intermediate grade
Large cell endocrine carcinoma	High grade
Small cell carcinoma	

the provision of data to analyze the primary site of the tumor, sites of metastasis and the possibility of considering systemic therapy for advanced disease.

2. Case description

A 36-year-old male presenting after the primary care physician noticed abnormally low potassium and complaints of feeling generally unwell. Though unable to clearly determine the time of onset, patient reported noticing loss of hair, worsening pedal edema and central obesity, facial plethora, generalized weakness, difficulty in standing from sitting position and weight gain followed by significant weight loss. These complaints were shortly followed by hypertension, diabetes, cushingoid

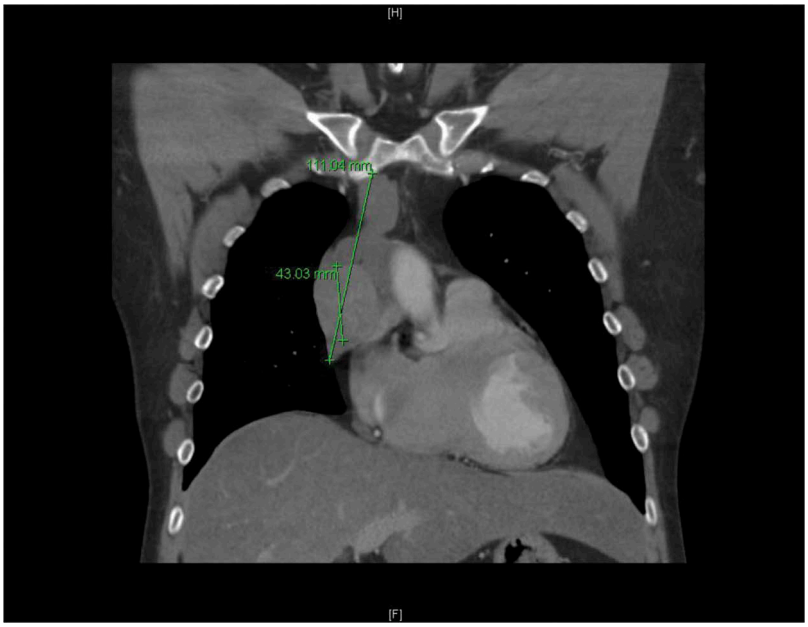

Figure 1. CT scan of the chest anterio-posterior view.

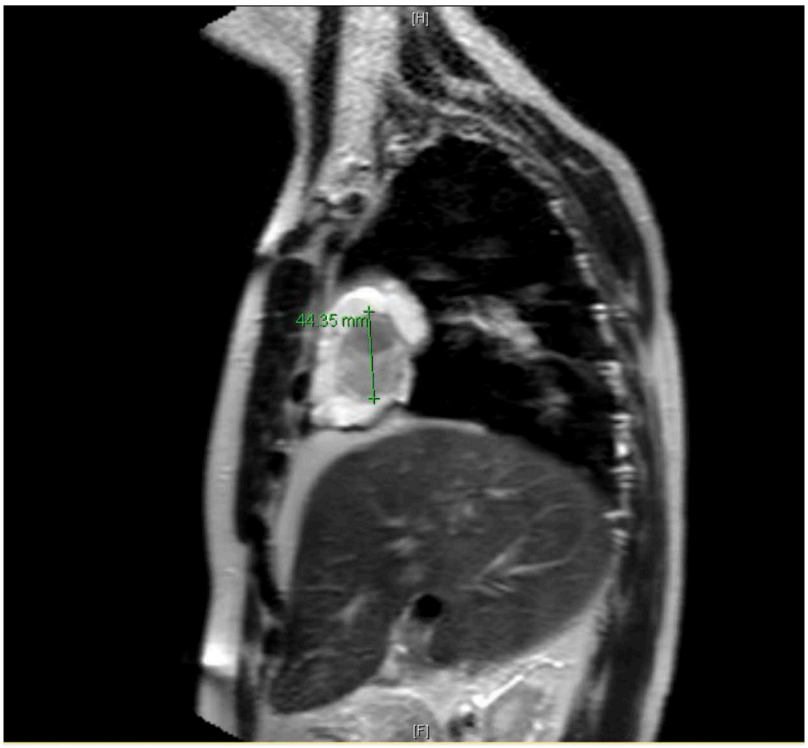

Figure 2. MRI lateral view.

features and hypokalemia. At the recommendations of his primary care physician, the patient presented to the hospital to have a more thorough evaluation. Initial blood chemistry revealed hyperglycemia of 294 mg/dl and severely low potassium of 2.4 mEq/L. Vital signs were within acceptable range of normal range except for the hypertension, while on metoprolol. Physical examination revealed centripetal obesity, supraclavicular and dorsocervical fat, periaxillary striae and purple abdominal striae greater than 4 mm. His cushingoid symptoms and the complete suppression of aldosterone collectively suggested endogenous Cushing's syndrome. Following a raised afternoon cortisol level of 28.2 μg/dl, adrenocorticotropic hormone (ACTH) was also noted to be high at 105.1 pg/ml after dexamethasone suppression test. He was started on oral twice a day replacement of 40 mEq potassium and spironolactone of 50 mg. Blood pressure control was achieved with metoprolol 100 mg extended release, amlodipine 10 mg daily, hydralazine 50 mg every 8 h and spironolactone. Insulin lantus 12 units with lispro 14 units pre-meal three times a day was able to control the high blood sugars. While the patient was still in the process of evaluation, he suffered a psychotic episode. He ran into a wall and was hallucinating. He later reported that, he thought he had murdered someone. The trauma work up with a CT scan of the chest revealed an antero-superior chest mass (Figure 1).

An MRI of the chest was obtained to better establish the relation between the mass and surrounding structures (Figure 2).

A mass measuring total 7.4 × 4.9 × 8.2 cm with a cystic and a central solid mass measuring 3.8 × 3.7 × 4.5 cm was seen. Initially, based on the radiological evidence, it was suspected to be a paraganglioma. A surgical intervention was sought for debulking and histopathological diagnosis. He was started on medical treatment for hypertension and hypokalemia while he waited for the surgical excision. Histopathology of the excisional biopsy revealed that he, in fact, was suffering from a thymic tumor. ACTH staining of the sample was noted to be positive, further confirming that the high levels of cortisol were the result of a cortisol secreting thymic NET.

3. Discussion

Thymic NETs present a diagnostic and a therapeutic dilemma. Because of the small number of cases observed, it is difficult to assess for the appropriation of current treatment modalities, development of new treatments, disease research prospects, diagnostic imaging value and development of surveillance protocols. This also leads to significant difficulty in allowing for observation of strong associations. NETs do not necessarily present with endocrinopathies; however, when reported, about 50% were seen to be hypercotisolism. The presence of cushingoid features along with an anterior mediastinal mass may serve as a red herring raising concern for further investigation.

Further, finding of an anterior mediastinal mass does not conclude the diagnosis. Thymic NETs need to be differentiated from other pathologies with a biopsy.

The exact mechanism of the psychosis was unclear in this case. Likely explanations could have been the high levels of cortisol and paraneoplastic or endocrine paraneoplastic syndromes. Because antibodies such as anti-Hu antibodies were not checked, it was unclear if paraneoplastic syndrome was the cause. However, neither could the high levels of cortisol be definitively held responsible for the change in mentation. It would be useful in such cases to check for these antibodies to guide treatment. Psychosis from high cortisol is an uncommon presentation with only a handful of cases reported. In clinical practice, however, high cortisol should raise the suspicion index especially if treatment is to be considered [14]. Use of mifepristone has shown some success in cases of psychosis secondary to hypercortisolism [15].

Treatment should be prompt if survival period is to be prolonged, and usually at a specialized center with the help of a multidisciplinary team approach. Surgical resection is thought to be superior and shown to have a better prognosis. Our patient received a complete thymomectomy therefore. Adjuvant and neoadjuvant radiation therapy (RT) has shown some promise in sub-totally resected and locally advanced unresectable non-metastatic disease. The use of medical management is mostly for symptomatic relief only, as in the case of our patient. Prognosis is highly unpredictable and dependent on surgical resectibilty, tumor stage, histologic grade and tumor size. Sasaoka stage was identified as a significant prognostic factor in a European-based study. Metastatic disease along with local recurrence has been seen even after resection, especially in aggressive (Atypical carcinoid or high grade) tumors. Overall, 5- and 10-year survival rates were noted to be 28 and 10%, respectively, following the largest North American 80 patient-based series. None of the high-grade tumors were disease-free after 5 years and 10-year survival rates were dependent on the tumor size, <7 cm 91% and >7 cm 29%.

Clustered families, with MEN-1 syndrome, are reported to have a higher incidence of thymic NETs. It could be useful to monitor these cases. Though no widely accepted surveillance protocols for high-risk patients and or cluster families exist, survival period shows a drastic decrease from 110 to 35 months in localized compared to metastatic disease. Therefore, development of a surveillance protocol will, most certainly, be beneficial for following families and individuals with the disease and associated syndromes. It is also recommended to extend surveillance past 5 years, since these tumors are very notorious for recurring even 20 years after resection. Limited number of cases makes the establishment of superiority among diagnostic and follow-up imaging

techniques a challenge, resulting in many proposed strategies. One such recommendation is yearly chest x-ray combined with triennial CT scans of the chest in high-risk individuals.

A rare presentation of a rare disease, such as our patient, will forever pose a diagnostic dilemma for physicians. It, however, also emphasizes the importance of a multidisciplinary team approach, to provide improved quality of patient care.

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