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) 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 thymectomy is recommended. Once the diagnosis of thymic NET is established, cross-sectional imaging with either indium-111 pentetreotide (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
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.

### Table 1. WHO classification for thymic neoplasms.

| Thymic neuroendocrine tumors                  | Grade  |
|----------------------------------------------|--------|
| Typical carcinoid tumors                     | Low    |
| Atypical carcinoid tumors                    | Inter  |
| Large cell endocrine carcinoma               | High   |
| Small cell carcinoma                         |        |

#### 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 features.

**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 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, amiodipine 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 hypercortisolism. 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 thymectomy 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 resectability, 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.

Disclosure statement
No potential conflict of interest was reported by the authors.

Funding
No funding source involved.

References
[1] Duh Q-Y, Hybarger CP, Geist R, et al. Carcinoids associated with multiple endocrine neoplasia syndromes. Am J Surg. 1987;154:142–148.
[2] Blayney DW. Thymic carcinoid and multiple endocrine neoplasia. West J Med. 1990;152:426.
[3] Frilling A, Becker H, Roehrer HD. Unusual features of multiple endocrine neoplasia. Henry Ford Hosp Med J. 1992;40:253–255.
[4] Goudet P, Murat A, Cardot-Bauters C, et al. Thymic neuroendocrine tumors in multiple endocrine neoplasia type 1: a comparative study on 21 cases among a series of 761 MEN1 from the GTE (Groupe des Tumeurs Endocrines). World J Surg. 2009;33(6):1197–1207. doi: 10.1007/s00268-009-9980-y.
[5] Teh BT, Zedenius J, Kyōtō S, et al. Thymic carcinoids in multiple endocrine neoplasia type 1. Ann Surg. 1998;228:99–105.
[6] Mari C, Léon J, Farrerons J, et al. Thymic carcinoid and parathyroid hyperplasia detection with 99mTc-MIBI men type 1. Endocrinol Invest. 1999;22:803–807.
[7] Satta J, Ahonen A, Parkkila S, et al. Multiple endocrine neoplastic-associated thymic carcinoid tumour in close relatives: octreotide scan as a new diagnostic and follow-up modality. Two case report. Scand Cardiovasc J. 1999;33:49–53.
[8] Goudet P, Cougard P, Calender A, et al. Clinical, surgical and genetic studies of 12 cases of thymic neuroendocrine tumors (Th-NET) among a cohort of 574 multiple endocrine neoplasia type 1 (MEN1) cases. Eighth International Workshop on Multiple Endocrine Neoplasia; 2002; Grand Rapids, MI, (Abstract 13).
[9] Christakis I, Qi W, Silva FAM, et al. Clinical features, treatments, and outcomes of patients with thymic carcinoids and multiple endocrine neoplasia type 1 syndrome at MD Anderson Cancer Center. Horm Cancer. 2016 Aug;7(4):279–287. Epub 2016 Jun 16.
[10] De Montpréville VT, Macchiarini P, Dulmet E. Thymic neuroendocrine carcinoma (carcinoid): a clinicopathologic study of fourteen cases. J Thorac Cardiovasc Surg. 1996;111:134–141. World Journal of Surgery, June 2009, Volume 33, Issue 6, pp 1197–1207.
[11] Trott MJ, Farah G, Stokes VJ, et al. A thymic neuroendocrine tumour in a young female: a rare cause of relapsing and remitting Cushing’s syndrome. Endocrinol Diabetes Metab Case Rep. 2016;2016:160018. Epub 2016 May 18.
[12] Wick MR, Scott RE, Li CY, et al. Carcinoid tumor of the thymus: a clinicopathologic report of seven cases with a review of the literature. Mayo Clin Proc. 1980;55:246–254.
[13] Lokich JJ, Li F. Carcinoid of the thymus with hereditary hyperparathyroidism. Ann Intern Med. 1979;89:364–365.
[14] Hirsch D, Orr G, Kantarovich V, et al. Cushing’s syndrome presenting as a schizophrenia-like psychotic state. Isr J Psychiatry Relat Sci. 2000;37(1):46–50.
[15] Bilgin YM, Van der Wiel HE, Fischer HRA, et al. Treatment of severe psychosis due to ectopic Cushing’s syndrome. J Endocrinol Invest. 2007 Oct;30(9):776–779.