ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS

Case Report

Unusual Chromogranin-A, TIF-1 Positive-Paraganglioma of the Head and Neck: A Case Report and Literature Review

Ramy Ibrahim[1]*, Jose R Hermann[2], Mehak Riaz[2], Kenneth S Roca[2], Amanda Arauz[2], Mina Salidis[2] and Rishit Arnav Shaquib[2]

[1]*Medical Director of Premier Medical Associates and Head of Research Department, USA*

[2]*Research Volunteer, Premier Medical Associates, USA*

***Corresponding Author:** Ramy Ibrahim, Medical Director of Premier Medical Associates and Head of Research Department, USA.

Received: January 19, 2023; **Published:** January 28, 2023

Abstract

Neuroendocrine tumors (NETs) comprise a group of rare tumors, especially when they are in the head and neck regions. Furthermore, it is unclear what is the optimal management for these tumors.

We present a case of an 80-year-old female patient with an asymptomatic swelling on the posterior neck, who underwent studies for pulmonary nodules that were present for more than 6 years. They were unchanged and negative for malignancy on bronchoalveolar lavage. A PET-CT scan showed indeterminate hypermetabolic subcutaneous masses within the posterior neck/upper chest on the right, as well as the anterior right shoulder region with the lung nodules suspected to be the primary tumor. The histopathology of the neck mass reported it to be a neuroendocrine tumor/carcinoma (NET/NEC). Initially, it was determined that it was a low-grade tumor, but later reported to be a high-grade Neuroendocrine tumor according to a Pathology report. The origin of this tumor was unclear, it was suggested to be a possible paraganglioma like medullary thyroid carcinoma or a neuroendocrine tumor of other origin.

Keywords: *Neuroendocrine Tumors (NETs); Paraganglioma; Chromogranin A (Cr-A); ITF-1; CT Scan; PET Scan*

Introduction

Neuroendocrine tumors are a diverse group of neoplasms that vary in biologic behavior, histologic appearance, and response to treatment. Several types of these neoplasms (e.g. well-differentiated neuroendocrine tumors of the tubular gastrointestinal tract [previously referred to as carcinoid tumors] and pancreas [pancreatic NETs or PNETs], medullary thyroid cancers, pheochromocytomas) are characterized by a slow growth and frequent secretion of hormones or vasoactive substances [1,2]. In most cases, these tumors also have a typical histologic appearance and are accurately diagnosed with standard pathologic methods (light microscopy and immunohistochemical staining). Others, as typified by small cell carcinoma of the lung, are highly aggressive neoplasms, classified as neuroendocrine carcinomas (NECs), and are usually in an advanced stage when they are diagnosed.

The term "neuroendocrine tumor" refers to well-differentiated neuroendocrine neoplasms, and "neuroendocrine carcinoma (NEC)" refers to poorly differentiated neuroendocrine cancers.

Various kinds of nomenclatures have been used to explain these neoplasms with limited consensus [1,2]. Thus, NETs have been divided into two broad groups:

1. NETs with epithelial differentiation: typical carcinoid (well differentiated), atypical carcinoid (moderately differentiated, including large cell carcinoma), and small cell carcinoma (poorly differentiated, including composite small cell carcinoma), and:
2. Neurally-derived tumors: paragangliomas, olfactory neuroblastomas [3].

It is worth to mention that an uncommon type of primary cutaneous small cell carcinoma (Merkel cell carcinoma) shows preference for the head and neck region. In rare cases, with the history of previous neuroendocrine cancer, NETs from other regions metastasize to the head and neck region [4,5].

Typical NETs, which are low-grade tumors with a low mitotic rate, are approximately four times more common than atypical NETs, which are intermediate-grade tumors with a higher mitotic rate and/or necrosis.

Epidemiology

Well-differentiated NETs are relatively rare tumors. In a series of 35,618 NETs (which included pancreatic NETs as well as gastrointestinal NETs [GINETs] at all sites) reported to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), the age-adjusted incidence for nonpancreatic primaries was 4.7 per 100,000 [5,6]. The annual incidence rate for African Americans was higher than for White Americans (6.46 versus 4.6 per 100,000), and the incidence for males was slightly higher than for females (4.97 versus 4.49 per 100,000). The median age at diagnosis for all patients with NETs was 63 years.

The incidence of well-differentiated NETs has been rising over time in the United States and elsewhere [4-7]. As an example, in an analysis of 64,971 NETs reported to the SEER registry, the age-adjusted incidence rate for all NETs raised from 1.09 to 6.98 per 100,000 between 1973 and 2012 [6]. This increase is probably due to increased and enhanced detection on radiographic imaging and endoscopy.

Case Report

We present the case of an 80-year-old female with past medical history of Hypertension, Hyperlipidemia, Chronic Obstructive Pulmonary Disease, Gastroesophageal Disease who presented with a history of smoking 1 PPD for nearly 30 years, with an asymptomatic posterior neck swelling on the right for the past 20 years with no constitutional signs or symptoms. The patient had an incidental finding of nodules on Chest X-rays done the previous years, for which the patient received a work-up with an initial CT scan that showed them to be pulmonary nodules. The patient was followed up with a yearly CT scan of the chest with no progression in size or appearance of the nodules. A subsequent CT scan showed mild bronchiectasis involving both lung bases, nodular consolidation within the left lower lobe anteriorly measuring 2.3 x 1.6 cm in size (Image 1), with nodularity within the medial segment of the right middle lobe, measuring 1.0 x 0.9 cm in size.

A PET scan (Image 2 and 3) done after the CT scan showed the pulmonary nodules to be stable and provided with the following findings:

- PET findings concerning for metastatic neuroendocrine tumor.
- There are multiple small and large lung nodules.
- The largest lung nodule within the left lower lobe demonstrates no significant activity, but likely represents the primary neuroendocrine tumor versus metastatic disease.
- 1 cm nodule within the medial segment of the right lower lobe demonstrating intense activity, which may represent the primary lesion.
- Additional subcentimeter lung nodules are noted.

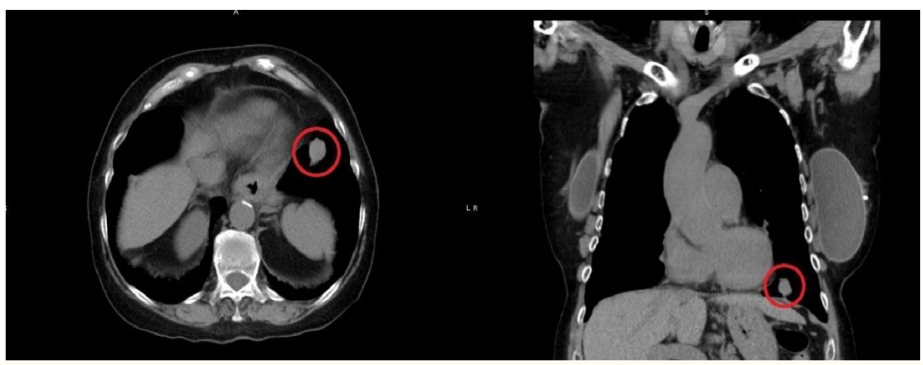

Image 1: *Nodular consolidation of the left lower lobe anteriorly measuring 2.3 x 1.6 cm in size.*

- Large subcutaneous soft tissue nodule within the posterior right neck and subcentimeter nodule within the right supraclavicular fossa consistent with metastatic lesions.
- No abdominal metastatic disease.
- 1.9 cm posterior right neck nodule with intense activity (Image 4), with a second subcutaneous nodule seen anteriorly in the right supraclavicular fossa measuring 6.6 mm with moderate activity.

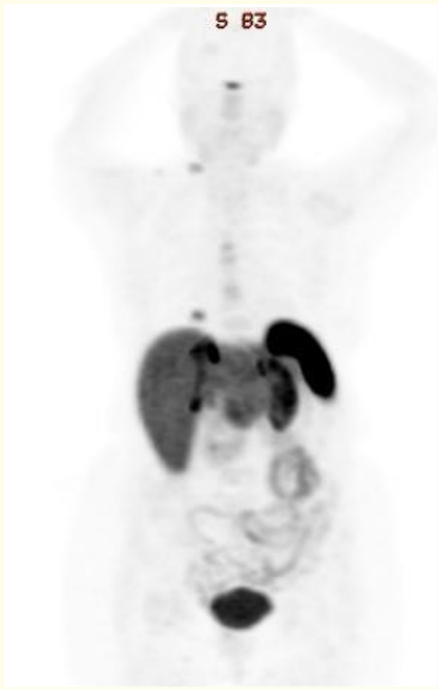

Image 2: *Anterior view of the PET scan showing the activity of various nodules.*

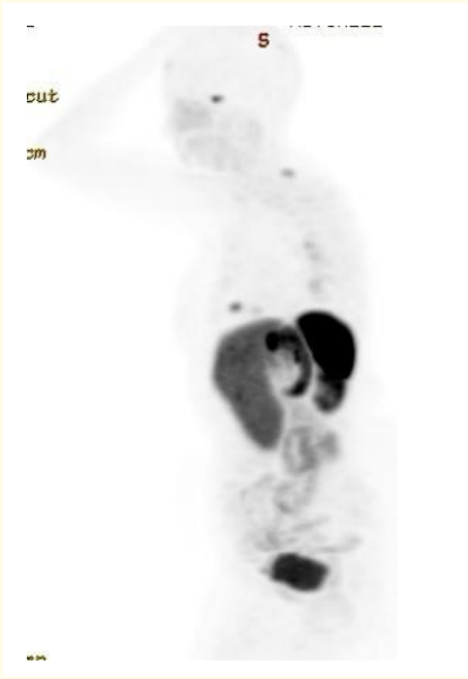

Image 3: *Lateral view of the PET scan showing the activity of various nodule in the lung and neck.*

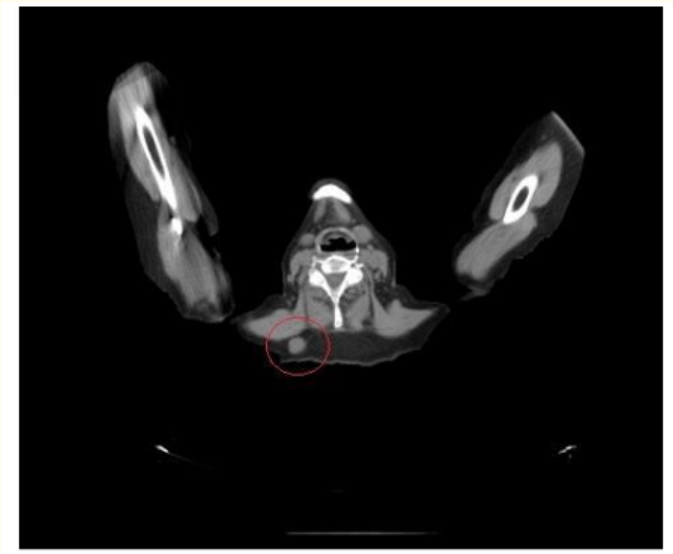

Image 4: *Posterior right neck nodule that showed intense activity on PET scan.*

The medical recommendation was to consider a follow up with an ultrasound and tissue sampling to exclude areas of malignancy at this site.

An ultrasound-guided fine needle aspiration of the right posterior neck nodule was performed and showed a low-grade Neuroendocrine tumor with organoid features. An immunohistochemical panel showed a positive Chromogranin-A and TTF-1, and a negative staining for CK7, CK20, MC and, CD10.

Ki67 IHC index was 5%. Urinary metanephrines were also negative.

The origin of this tumor was unclear, and it was suggested to be a possible paraganglioma, thyroid medullary carcinoma or a neuroendocrine tumor of other origin. The case was referred for further specialty consultation.

Two weeks after the finding mentioned previously, a right neck biopsy was performed and showed:

- Tissue cores wholly comprised of a neoplastic proliferation with organoid or cell next growth separated by fibrovascular stroma and composed of cells with round to oval nuclei, dispersed/stippled to hyperchromatic appearing nuclear chromatin, inconspicuous nucleoli and clear to slightly eosinophilic cytoplasm with indistinct borders.
- Mild nuclear pleomorphism with no identifiable mitotic figures. In the submitted slides there were no identifiable normal tissue structures. The submitted immunohistochemistry-stained slides showed the neoplastic cells to be positive for chromogranin A and transcription intermediary factor 1 (TTF1), but negative for cytokeratin's (MCK; CK7; CK20) and CD10.
- No significant increase in the proliferation rate as seen in the submitted Ki67 stained slide.

The findings were diagnostic for neuroendocrine tumor (NET) and given the pattern of growth, presence of immunoreactivity for neuroendocrine markers in particular chromogranin A and absence of immunoreactivity for cytokeratin's, the findings were consistent with a paraganglioma. The absence of cytokeratin immunoreactivity weighed against a possible diagnosis of medullary thyroid carcinoma, a NET G1 (formerly referred to as carcinoid tumor) or NET G2 (formerly referred to as atypical carcinoid tumor). The findings were those of a high-grade NET or of a neuroendocrine carcinoma. Additional confirmatory immunostaining including but not limited to synaptophysin, Insulinoma-associated protein 1 (INSM1), GATA3 and Succinate Dehydrogenase B (SDHB) were suggested.

SDHB immunohistochemical staining is important in paragangliomas as the loss of SDHB immunohistochemical staining occurs in the vast majority of paragangliomas with germline mutation in any of the succinate dehydrogenase (SDH) genes and is often found in patients with hereditary paraganglioma. Further, paragangliomas associated with SDHB mutations have a high risk of metastasis. Retained SDHB expression would weigh against hereditary paraganglioma. The lesion was located "within the right posterior neck" and the imaging findings stated it was a hypermetabolic mass in the lower neck/upper back on the right. The stated location is not a usual site for head and neck (parasympathetic) paraganglioma which tend to occur in relationship to the carotid body (carotid body paraganglioma), middle ear (jugulotympanic paraganglioma) and vagal nerve trunk (vagal paraganglioma) and less likely in other locations. Nevertheless, the findings seen in the submitted slides supported a diagnosis of a paraganglioma. The patient also had a lung nodule on several imaging studies from the previous years, but whether there is a relationship between the right posterior neck mass and a lung nodule is purely speculative.

Finally, the patient had a follow-up with her Oncologist, and at that time complained of extreme fatigue, lethargy, effort intolerance, and deconditioning. The patient was recommended an octreotide scan and a follow up to review the results. She was also referred for a surgical consultation for a wide local excision of the lesion on the upper back.

Discussion

The incidence and prevalence of neuroendocrine tumors (GEP-NETs) has been incrementing progressively [7]. They have been historically taken together as a homogeneous group under one broad term based on a single shared characteristic such as the expression of neuroendocrine markers, one of them being Chromogranin-A (which was positive in our patient) and Syn, which might probably have no impact in terms of management or clinical prognosis [8,9].

Although NETs tend to present with liver metastases as their initial presentation, and most of them are gastroenteropancreatic NETs [10], our patient presented with a different primary site (head and neck) and did not have any metastases according to the studies performed. She had a positive Chromogranin A and TIF-1 which is generally expressed in most poorly differentiated NECs and some well differentiated NETs with lung etiology. Our case is out of the normalcy for this immunohistochemistry as one of the known disadvantages from TIF-1 is that it can also be found in other extrapulmonary poorly differentiated NECs [11] and the patient had a NET located on the head/neck area supporting this "disadvantage".

Paragangliomas are neoplasms that have their origin from extra adrenal chromaffin cells of the sympathetic and parasympathetic paraganglia; in the neck, it can be inferred -almost as a rule- that paragangliomas arise from the parasympathetic paraganglia.

The initial assessment should consist of imaging of the affected area (if any has been identified), chest, abdomen, and pelvis (either CT or MRI) [12]. Considering the high metabolic rate of these poorly differentiated NECs, performing a PET scan is also a sensitive imaging modality [13]. Due to a high risk of central nervous system metastases, a Brain MRI is highly recommended.

The management of paraganglioma is based on surgical resection, with a careful perioperative management with alpha- and beta-adrenergic blockade in hormonally active paragangliomas (negative in our case). Most of these tumors are benign, but for patients with malignant disease, radiation and chemotherapy may offer a discrete benefit. Long-term follow-up is vital, as paragangliomas may recur years after the initial diagnosis [14]. Ongoing research focus on the genetic foundation of this tumor will allow for targeted molecular therapies in the future.

Conclusion

Paragangliomas of the head and neck are rare, they are considered benign when they are confined to their region and site of origin [15]. The patient presented had an unusual presentation of a Neck mass that required multiple imaging and laboratory studies that concluded that the patient had a Paraganglioma. The overall assessment requires a very careful and meticulous evaluation of imaging studies such as X-rays, CT scans, PET scans, and -in some cases- MRI. It is also imperative to include immunohistochemistry, although their use has been better established as a prognostic (cellular differentiation) and staging tool. The initial management of a paraganglioma should be focused on a complete surgical removal of the area considered to include the primary tumor and regional lymph nodes, which the patient will have scheduled.

This case clearly states the importance of following up on lung nodules seen in low-cost studies such as a Chest X-ray. CT scans are of vital importance to detect conditions that are not commonly found or suggest the onset of a disease. We expect the patient to have a successful outcome from this rare presentation of a suspected paraganglioma.

Bibliography

1. Ferlito A., *et al*. "Neuroendocrine neoplasms of the larynx: an overview". *Head Neck* 31 (2009): 1634-1646.

2. Kusafuka K., *et al*. "Large cell neuroendocrine carcinoma of the head and neck". *Oral Oncology* 48 (2012): 211-215.

3. Barnes L editor. "Neuroendocrine tumours". Lyon: IARC Press (2005).

4. Subedi N., *et al*. "Neuroendocrine tumours of the head and neck: anatomical, functional and molecular imaging and contemporary management". *Cancer Imaging* 13.3 (2013): 407-422.

5. Rindi G., *et al*. "A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal". *Modern Pathology* 31 (2018): 1770.

6. Klimstra DS., *et al*. "Classification of neuroendocrine neoplasms of the digestive system". In: WHO Classification of Tumours: Digestive System Tumours, 5th edition, WHO Classification of Tumours Editorial Board (Edition), International Agency for Research on Cancer, Lyon (2019): 16.

7. Castellano D., *et al*. "Future perspectives on neuroendocrine tumors". *Cancer and Metastasis Reviews* 30.1 (2011): 35-40.

8. Oronsky B., *et al*. "Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas". *Neoplasia* 19.12 (2017): 991-1002.

9. Strosberg JR., *et al*. "North American Neuroendocrine Tumor Society (NANETS) The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas". *Pancreas* 39.6 (2010): 799-800.

10. Riihimäki M., *et al*. "The epidemiology of metastases in neuroendocrine tumors". *International Journal of Cancer* 139 (2016): 2679.

11. La Rosa S., *et al*. "TTF1 expression in normal lung neuroendocrine cells and related tumors: immunohistochemical study comparing two different monoclonal antibodies". *Virchows Archiv* 457 (2010): 497.

12. Pavel M., *et al*. "ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary". *Neuroendocrinology* 95 (2012): 157.

13. Hicks RJ. "Use of molecular targeted agents for the diagnosis, staging and therapy of neuroendocrine malignancy". *Cancer Imaging* 10 (2010): S83.

14. Joynt KE., *et al*. "Paragangliomas: etiology, presentation, and management". *Cardiology in Review* 17.4 (2009): 159-164.

15. Lee JH., *et al*. "American College of Surgeons Commission on Cancer; American Cancer Society. National Cancer Data Base report on malignant paragangliomas of the head and neck". *Cancer* 94.3 (2002): 730-737.

Volume 6 Issue 2 February 2023