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Case Report

Uterine Sarcoma Presenting as Hypercapnic Respiratory Failure

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Thyroid metastasis · Metastatic sarcoma · Hypercapnic respiratory failure · Uterine sarcoma

Abstract
Thyroid cancer is a type of malignancy that is considered to have a low morbidity and an indolent disease course in most patients. Though some of its pathologic variants such as anaplastic carcinoma may present with advanced disease staging, it is important to consider the possibility of metastasis to thyroid which may present like a thyroid primary. Solid organ carcinomas form the bulk of the uncommon metastasis to the thyroid, though sarcomas from various organs also rarely exhibit this activity. Literature demonstrating sound diagnostic criteria for these occurrences is sparse. We present a case of uterine sarcoma with distant metastasis to the thyroid gland that initially presented as hypercapnic respiratory failure. Only an inpatient episode of uterine bleeding prompted our team to explore the potential of a metastatic process. Our diagnosis was made utilizing a multidisciplinary approach that we feel is important for clinicians dealing with metastatic disease to the thyroid. In addition to sound physical exam, and use of appropriate imaging modality, we feel it is essential to utilize a detailed cytohistologic specimen evaluation, immunohistochemistry, and genetic sequencing to effectively work up such patients. Although our patient did not survive her hospital stay, we hope this paper brings greater awareness of this malignancy and acts as a benchmark for diagnosing such an unusual remote primary.

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Introduction

Thyroid cancer is believed to be one of the least deadly human cancers [1]. In fact, the United States Preventive Services Task Force (USPSTF) has changed their guidelines in recent years to recommend against screening for thyroid cancer in asymptomatic patients. For those identified as low risk, screening for thyroid cancer does not improve mortality. Alternatively, the thyroid cancers associated with greater mortality risk are fast growing and usually present symptomatically before screening can be utilized [2]. Typically, this is the case with anaplastic thyroid carcinoma, its median overall survival is estimated to be 4 months, and the disease-specific mortality is nearly 100% [3]. Patients with anaplastic thyroid carcinoma usually present with a rapidly growing, invasive neck mass, cervical lymph node involvement, and possibly distant metastasis [3]. Patients with thyroid metastasis have also been found to present in a similar manner. One study found that metastasis to thyroid presented in 72% of patients as a rapidly enlarging thyroid mass [4].

In cases of thyroid malignancy, the possibility of metastasis to the thyroid must be considered. Thyroid metastasis accounts for 0.36% of all thyroid malignancies. The common primary sites that metastasize to thyroid are kidney, lung, lower gastrointestinal tract, and breast [5]. A diagnostic dilemma ensues when a thyroid mass is sampled prior to the diagnosis of the tumor primary. In such cases, immunohistochemical staining and patient symptomatology may aid in identification of the primary malignancy. Sarcomas are primary malignancies that rarely exhibit such distant spread to the thyroid gland [6]. A study estimates the incidence of sarcoma metastasis to the thyroid as 2% of all cases of metastatic disease of the thyroid [6]. We present a case of a thyroid mass that posed this clinical and diagnostic dilemma.

Case Presentation

A 63-year-old female presented to our institution in respiratory distress and hypercapnic respiratory failure requiring intubation. Patient was found to have a large, firm immobile mass in the submandibular area as demonstrated on CT (Fig. 1). Patient underwent multiple biopsies for pathologic evaluation. Pathology results favored a malignant mesenchymal neoplasm.

The thyroid mass did not demonstrate typical histocytomorphologic characteristics of a primary thyroid malignancy and favored sarcoma over anaplastic thyroid carcinoma, though the latter could not be excluded entirely. The tumor cells were positive for vimentin, CD34, caldesmon and focally positive for SMA. The type IV collagen showed a distinctive membranous pericellular pattern of staining, increasing suspicion for a primary glomangiosarcoma or angiosarcoma rather than primary thyroid carcinoma (Fig. 2). In addition, tissue sample was also sent for next generation sequencing (NGS) which identified mutations of RECQL4, PDGFRB, NRG1, MYC, and MED12.

During the patient's hospital stay, she had an episode of postmenopausal uterine bleeding. CT abdomen pelvis was performed at that time, which identified a diffusely enlarged heterogeneous uterus with thickened endometrium (Fig. 3).

The finding on CT abdomen pelvis, along with the abnormal uterine bleeding, indicated the primary malignancy may likely be uterine. Further evaluation of the results of immunohistochemical staining and NGS point mutations suggest the primary malignancy as uterine leiomyosarcoma (LMS).

During her hospital course, maintaining an airway was problematic. Friability of the tumor made securing a tracheostomy tube incredibly difficult. The patient required two

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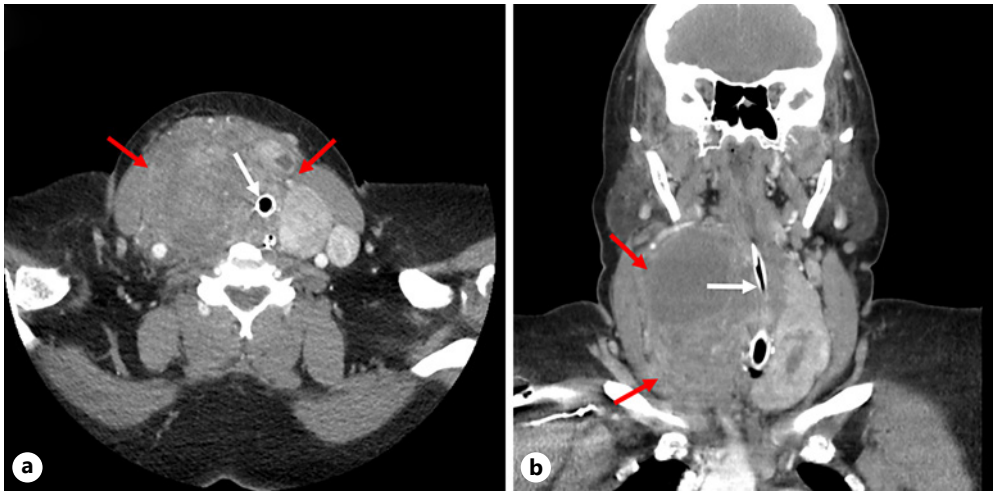

Fig. 1. Contrast-enhanced CT soft tissue neck axial image (**a**) and coronal reformatted image (**b**) demonstrating a large solid and cystic mass centered in the right thyroid lobe with extension into the isthmus and significant mass effect (red arrows) including displacement of the trachea to the left of midline (white arrow).

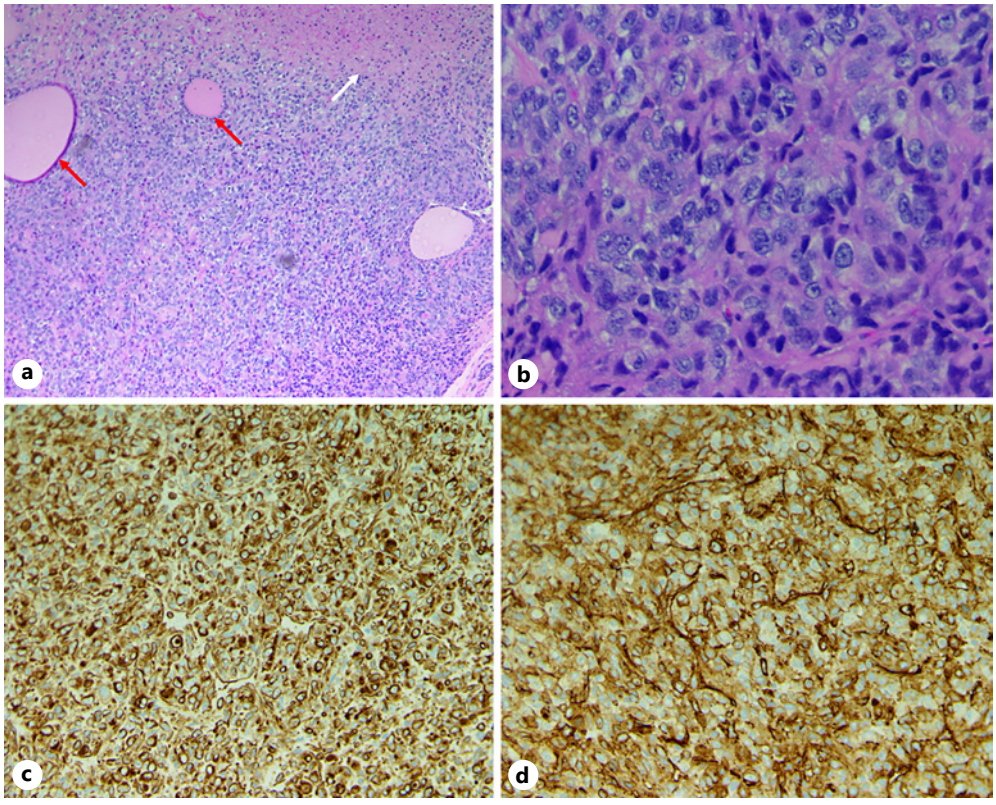

Fig. 2. Histology sections and immunohistochemical evaluation of thyroid tumor. **a** Sheets of tumor cells surrounding benign thyroid follicles (red arrows), tumor necrosis (white arrow) (H&E stain, ×4). **b** Higher magnification, tumor cells appear epithelioid with prominent vesicular nuclei and occasional prominent nucleoli (H&E stain, ×20). **c**, **d** Tumor cells are diffusely positive for vimentin and CD34, respectively.

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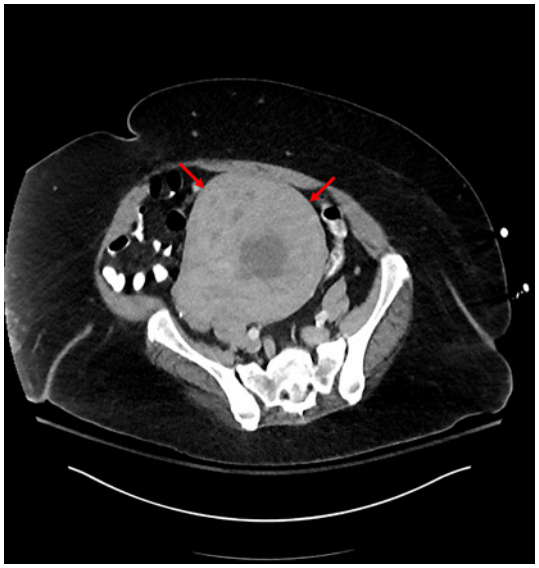

Fig. 3. Contrast-enhanced CT scan of the pelvis demonstrating a large and heterogeneous uterus with thickened endometrium (red arrows).

surgical procedures to establish an airway with multiple bronchoscopy-assisted cricothyrotomy tube repositioning to resecure a definitive airway. Due to advanced presentation of her disease, the patient ultimately did not survive her hospital stay.

Discussion

NGS identified mutations consisting of RECQL4, PDGFRB, NRG1, MYC, and MED12. The NGS report described PDGFRB mutations have been seen in myofibromas, myofibromatosis, one LMS, and a prostatic adenocarcinoma. PDGFRB mutations may also be seen in uterine sarcomas, gliomas, and lung cancers and they are rare in thyroid neoplasms [7].

Our patient was found to have the point mutation variant MED12 p.Gly44Cys. NGS reporting described this variant in uterine leiomyomas, breast fibroadenomas, and uterine LMSs. MED12 is believed to be a useful biomarker for uterine LMS. It has been reported that MED12 mutations are rarely observed in other sarcomas and even extrauterine LMSs [8].

Immunohistochemical staining in our case demonstrated positivity for vimentin, CD34, CD68, CD56, caldesmon, MYC, actin, type IV collagen, factor VIII with a high Ki67 index. Immunohistochemical staining and NGS studies were helpful in determining the lineage of this patient's malignancy. Initially, a primary thyroid malignancy was ruled out by staining for the thyroid-specific markers. Anaplastic thyroid carcinoma typically stains positive for PAX8 and cytokeratin while TTF-1 and thyroglobulin are almost entirely negative [5, 9, 10]. None of the thyroid-specific markers were positive in our case.

A strong differential for our patient's primary malignancy was LMS. Case reports of uterine LMSs, specifically those that metastasized to the thyroid, were reviewed. Immunohistochemical staining in these cases is typically positive for alpha smooth muscle actin (SMA), desmin, h-caldesmon, and vimentin and negative for cytokeratin, thyroglobulin, calcitonin, and S-100 protein [10, 11]. One case report of a metastatic LMS described a fine needle aspiration with cytology results that demonstrated features which raised suspicion for a malignant tumor of mesenchymal origin [10]. The immunohistochemical staining in this case was positive for smooth muscle actin and desmin. A second case report, specific to uterine LMS

with metastasis to the thyroid, reported tumor cells staining positive for SMA and desmin and negative for cytokeratin and thyroglobulin. The patient described in this case also presented with abnormal uterine bleeding. After total abdominal hysterectomy with bilateral salpingo-oophorectomy, samples stained positive for SMA, desmin, epithelial membrane antigen (EMA), and caldesmon [9]. An additional case report of a metastatic LMS with metastasis to the thyroid demonstrated desmin and smooth muscle actin positivity and cytokeratin, S-100, CD10, and EMA negativity. The same results of IHC staining were found in the thyroid lesion [12]. Additionally, a study that evaluated 78 LMS tissue samples found that smooth muscle actin was the most sensitive immunohistochemical stain for LMS. Other highly sensitive markers included calponin, desmin, caldesmon, and myosin [13–15]. The IHC positivity for SMA, caldesmon, and vimentin in our sample supports the likelihood of LMS as the primary malignancy.

Based on the cytohistomorphologic features and the immunohistochemical staining profile, other possible differentials included undifferentiated endometrial sarcoma, Carcinoma Showing Thymus-Like differentiation (CASTLE), Spindle Epithelial Tumor with Thymus-Like differentiation (SETTLE), and epithelioid angiosarcoma of the uterus. Although rare, review of literature identified 1 case of undifferentiated endometrial sarcoma with metastasis to thyroid. This case described immunohistochemistry staining that was negative for AE1/AE3, thyroglobulin, calcitonin, smooth muscle actin, CD45, estrogen receptors, progesterone receptors, TTF-1, and CD34. These neoplastic cells were found to be positive for CD10 and vimentin [16]. This contrasts the immunohistochemical staining profile in our patient.

SETTLE can mimic the cytomorphology seen in LMS [10, 17]. However, when immunohistochemistry staining is performed, they are typically positive for cytokeratin [10]. Thyroid carcinomas (i.e., CASTLE, SETTLE) were also excluded by morphology and immunophenotype.

A primary epithelioid angiosarcoma of the uterus has also been described with immunohistochemical staining positive for CD31, factor VIII, ERG, cytokeratin, and variable expression for CD34. Actin and desmin are muscle markers and are typically negative. AE1/3 indicates carcinoma, which would also be negative. Less than 25 cases of uterine angiosarcoma have been reported in literature [18–20]. Angiosarcomas stain positive for von Willebrand factor (factor VIII), CD34, CD31, and VEGF [21].

Although our thyroid lesion demonstrates positivity for some IHC stains which are positive in angiosarcomas, uterine angiosarcomas are extremely rare. Because of the rarity of this presentation, it would be highly unlikely that a uterine angiosarcoma metastatic to thyroid was the cause of presentation in our patient. Uterine LMSs metastasis to thyroid is also a rare event. However, in view of the immunohistochemical staining, NGS results, the clinical presentation of our patient, and the published diagnostic data in the literature, a uterine LMS primary is most likely.

There are fewer than 20 metastatic LMS of the thyroid gland reported in the literature and only 8 reported to have a uterine primary [9, 10]. Our patient's presentation demonstrated by acute airway compromise and hypercapnic respiratory failure posed an interesting diagnostic dilemma both because of the rarity of the pathology and the urgency to establish treatment options. It has been reported that metastasis to thyroid is associated with a poor prognosis [9]. However, there has been no mention in the literature of a patient's initial presentation for metastatic thyroid malignancy, presenting as hypercapnic respiratory failure requiring intubation.

Our case was limited by inability to further evaluate the uterine mass. This would have allowed a more definitive diagnosis. However, we feel our specimen evaluation with immunostaining and NGS analysis was sufficient in developing a diagnosis.

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Conclusion

Uterine sarcoma with metastasis to the thyroid gland is both a rare occurrence and a rare indication for emergent medical care secondary to acute hypercapnic respiratory failure. One must utilize cytohistologic specimen evaluation, immunohistochemical staining, and NGS analysis to effectively diagnose this pathology. With limited data on this subject, this case aims to provide more definitive diagnostic criteria that may be utilized in future clinical practice.

Statement of Ethics

Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. The privacy and confidentiality of the patient's personal information was protected. Submission of research protocol to an Institutional Review Board is not required for a single case in our institution. Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and University of Florida Health-Jacksonville Ethics Committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Kimberly Boldig wrote the introduction, case presentation, discussion, conclusion, and references. Matthew Montanarella wrote the abstract, selected and edited radiographic imaging, and edited the manuscript. Noor Marji and Anwer Siddiqi were senior editors and arranged pathology slides with corresponding figure legends.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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