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Case Report

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Adamantinoma-Like Ewing Sarcoma of the Thyroid: Case Report and Literature Review

Crisafulli Gregory, MD[1], Trivedi Aakash, DO[1], Bittar Noor, MS[1], Ankudey Edem[1], Akmal Amer, MD[2] and Christian Derick, MD[1]

[1]*Department of Surgery, St. Joseph's University Medical Center, Paterson, NJ, USA*

[2]*Department of Pathology, St. Joseph's University Medical Center, Paterson, NJ, USA*

Abstract

Adamantinoma-Like Ewing Sarcoma (ALES) is an exceptionally rare tumor, traditionally classified as a variant of Ewing Sarcoma due to the presence of the EWSR1-FLI1 translocation. Predominantly affecting the head and neck, particularly the parotid gland, ALES exhibits a slight female predominance. Adamantinomas and Ewing sarcomas differ significantly in their origin, histology, and clinical presentation. This case report presents a unique instance of ALES originating in the thyroid gland, marking the first documented case of thyroid ALES incidentally presenting with abdominal pain. A 39-year-old male with a complex medical history presented with acute right upper quadrant abdominal pain. Initial evaluation for suspected hepatobiliary disease revealed a liver mass and an asymmetrically enlarged thyroid with a suspicious nodule. Subsequent imaging and biopsy confirmed the diagnosis of ALES in the thyroid. The patient underwent a total thyroidectomy and is now under multidisciplinary care, with plans for further surgical and chemoradiation therapy. Histopathological analysis, including immunohistochemical staining and RT-PCR, confirmed the EWSR1-FLI1 fusion, solidifying the diagnosis. This case underscores the importance of including ALES in the differential diagnosis of thyroid masses and highlights the urgent need for further research to develop standardized diagnostic and treatment protocols for this rare and challenging malignancy.

Keywords

Adamantinoma-Like Ewing Sarcoma, Thyroid tumor, EWSR1-FLI1 translocation

Introduction

Adamantinoma-Like Ewing Sarcoma (ALES) is an exceptionally rare tumor, historically classified as a variant of Ewing Sarcoma because it classically harbors an EWSR1-FLI1 translocation. With only approximately 64 cases documented in the literature, ALES predominantly occurs in the head and neck region and exhibits a slight female predominance, with an estimated male-to-female ratio of 1:1.6. The peak incidence is in the fifth decade of life with the majority of cases arising in the parotid. We report a rare instance of ALES originating in the thyroid gland, and to our knowledge, it is the first case of thyroid ALES incidentally discovered in a patient presenting with abdominal pain.

Case Presentation

A 39-year-old male presented to the Emergency Department (ED) for acute right upper quadrant abdominal pain after being seen by his primary care physician a week prior for viral gastroenteritis. His social and medical history included a 25-pack-year smoking history, obesity, and extensive hepatobiliary disease including a history of cholelithiasis, cholecystitis, hepatolithiasis treated with multiple endoscopic retrograde cholangiopancreatographies (ERCPs), intra/extrahepatic ductal dilatation, hemobilia, liver cyst, as well as adrenal incidentaloma. On presentation to the ED, the patient's lab findings were notable for leukocytosis of 12.2/mm^3, hypocalcemia (Ca 7.8 mg/dL), hyperbilirubinemia (total bilirubin 6.6 mg/dL, direct bilirubin 4.5 mg/dL), elevated alkaline phosphatase (209 units/L), and transaminitis (ALT 147 units/L, and AST 132 units/L). Lipase, urinalysis, blood cultures, and viral PCR serology were unremarkable. The patient was admitted for further evaluation and management. Malignancy workup was initiated and revealed an elevated

***Corresponding author:** Crisafulli Gregory, MD, Department of Surgery, St. Joseph's University Medical Center, Paterson, NJ, USA

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CA 19-9, which showed a significant increase from 200 to 7380 over the course of 9 days, raising suspicion for cholangiocarcinoma.

A CT scan of the abdomen and an ultrasound of the right upper quadrant were performed to evaluate the patient's abdominal pain, revealing a 1.2 cm simple liver cyst and cholelithiasis. The liver cyst was also identified on a subsequent MRI of the abdomen and MRCP. While concerning for potential metastasis, the cyst was too small to undergo CT-guided biopsy. A CT Thorax was completed to rule out metastasis and showed asymmetric enlargement of the left thyroid lobe with suggestion of a hypodense nodule along with mildly enlarged paratracheal lymph nodes. He then underwent an ultrasound of the thyroid which showed a left lower pole nodule measuring 2.8 cm × 2.4 cm × 3 cm in dimensions with a volume of 10.8 mL, hypoechoic, taller than wide, irregular mass with internal calcifications corresponding to Thyroid Imaging Reporting and Data System (TIRADS) category 5. Subsequent fine-needle aspiration of the left lower pole of the thyroid nodule showed hyperchromatic nuclei and granular chromatin. Based on these findings, the differential diagnosis included medullary thyroid carcinoma versus poorly differentiated thyroid carcinoma. A follow-up CT of the neck was performed two months later and showed a 4.4 cm × 2.8 cm × 4.3 cm mass arising from the left lobe of the thyroid with extension into the anterior superior mediastinum with no associated metastatic neck adenopathy, a significant increase in tumor size from baseline. The right lobe of the thyroid and isthmus showed no additional masses. An additional CT thorax with contrast, performed the same day, showed abnormal mass-like hypodense appearance of the left thyroid lobe with abnormal heterogeneous enhancement with re-demonstration of neck lymphadenopathy.

Given the rapid growth, the patient underwent a total thyroidectomy and partial resection of the left strap muscle due to local invasion. It was noted intra-operatively that the mass was seen invading the paratracheal space and the carotid sheath. The posterior margin of the specimen showed gross residual disease. He tolerated the surgery well and was discharged home with a Jackson-Pratt drain which was removed four days later.

Histopathologic analysis of the resected specimen revealed a malignant small round blue cell tumor involving the thyroid parenchyma of the left lobe (Figure 1 and Figure 2). Immunohistochemical studies showed positive staining for pan-cytokeratin, CAM 5.2, CK AE1/AE3, p40, FLI-1, and membranous staining for CD99, with focal positivity for synaptophysin. The tumor was negative for NUT, CD5, PAX-8, TTF-1, and chromogranin. Thyroglobulin testing was non-diagnostic. The specimen was sent to Memorial Sloan Kettering Cancer Center, New York, for further analysis. RT-PCR was performed and demonstrated the presence of an EWSR1-FLI1 fusion. Taken together, based on the clinical and pathological findings, a diagnosis of ALES of the thyroid was made.

Currently, the patient is under multidisciplinary outpatient care, with plans for diagnostic laparoscopy to further evaluate his liver mass, additional surgical intervention from a head/neck specialist, and possible adjuvant chemoradiation therapy for his thyroid ALES.

Discussion

Adamantinoma-Like Ewing Sarcoma was first identified in 1999 by Bridge, et al. and is a rare and scarcely reported malignancy [1]. Adamantinomas are low-grade bone tumors, most commonly affecting the tibia, characterized by biphasic histology of epithelial and osteofibrous components. In contrast, Ewing sarcoma is an aggressive mesenchymal tumor composed of small round cells, affecting both bones and soft tissues, primarily the pelvis, axial skeleton, and extremities, with only 3% to 9% of cases occurring in the head and neck [2,3]. ALES, also referred to as "Carcinoma with Ewing

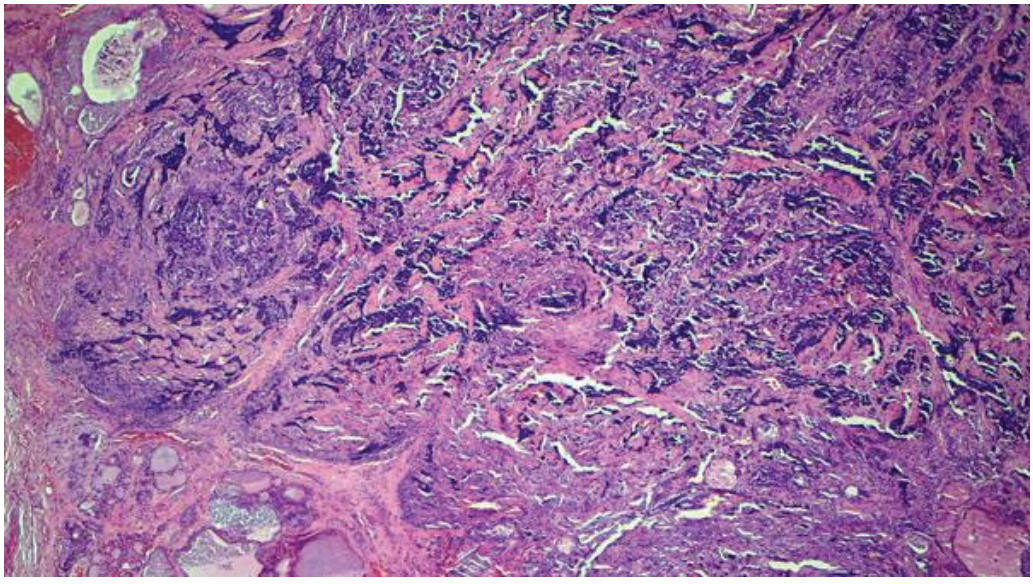

Figure 1: Nests and lobules of basaloid cells with few follicular formations.

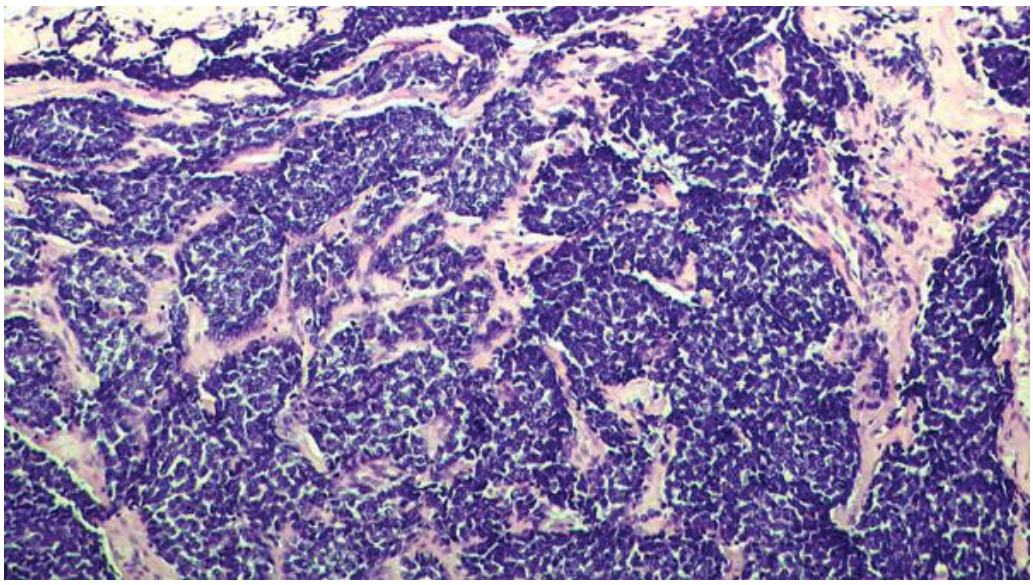

Figure 2: Round to oval nuclei with fine granular chromatin and minimal cytoplasm.

Family Tumor Elements" (CEFTE), predominantly involves the head and neck, primarily in the parotid gland, and rarely in the thyroid gland [4-14]. Our case represents an atypical presentation of ALES of the thyroid gland as an incidental finding in a patient with abdominal pain.

The clinical presentation of ALES varies depending on its location. For example, sinonasal cases often present with oral pain and swelling, while parotid or salivary gland cases typically manifest as enlarging facial masses. The effect of ALES on soft tissue of the neck may present with Horner syndrome and neck masses with or without pain. Thyroid ALES most commonly presents with either a painful or painless neck mass, unlike in our patient [9]. Only one previous case describes abdominal pain as the presenting symptom, which was a case of ALES of the pancreatic tail [15].

Appropriate diagnosis is imperative for effective management, yet an estimated 62% of cases are initially misdiagnosed [16]. Histopathologically, ALES is characterized by malignant small round blue cells with fine chromatin, prominent nucleoli, and hyalinized stroma. This presentation is likely the reason behind the common misdiagnosis of ALES as other small round blue cell tumors such as small cell carcinoma, alveolar rhabdomyosarcomas, olfactory neuroblastomas, lymphoma, or melanomas [17]. Given the broad histologic differential, immunohistochemical staining is key to diagnosis of ALES. Nearly all reported cases are positive for CD99, p40, and CK AE1/AE3 [16,18]. Previous authors have argued that if a tumor shows positivity for p40, p63, and synaptophysin, then ALES should be strongly considered. Additionally, if a tumor shows CD99 positivity, then molecular studies to evaluate for the EWSR1 rearrangements should be promptly pursued [19].

Many authors have shed light on the classification dilemma of ALES. That is, whether ALES is a true sarcoma with carcinoma-like features or a carcinoma that harbors the EWSR1-FLI1 fusion [5,12,18,20]. Perhaps the leading reason behind the subclassification of ALES under Ewing Sarcoma is that ALES harbors an EWSR1-FLI translocation. Recently, however, multiple reports have shown EWSR1-negative ALES cases, and ALES cases with FUS-FLI1 fusions [6,21]. Fritchie, et al. compared DNA methylation patterns between ALES tumors and classic Ewing Sarcoma and showed that all studied ALES cases shared a distinct DNA methylation cluster pattern that differed from traditional Ewing Sarcoma [6]. Meanwhile, Chatzopoulos, et al. compared RNA expression profiles of two ALES tumors (both harbored the EWSR1-FLI1 translocation) to four traditional Ewing Sarcoma cases and two non-neoplastic thyroid tissue cases, and showed that the ALES tumors uniquely expressed 137 genes, many of which strongly expressed squamous epithelial differentiation, further supporting ALES as a unique disease entity with features of both carcinoma and sarcoma [7].

There is no established association between systemic disease and the development of ALES. However, a review by Lauricella, et al. demonstrated that 14% of patients with salivary gland ALES had a history of papillary thyroid cancer, and 10% of patients had a history of ductal breast cancer [16]. To date, no cases of ALES involving the liver have been reported, although rare cases of primary hepatic Ewing sarcoma do exist [22]. The role of the elevated CA 19-9, as seen in our patient, is unclear, as normal levels were observed in a case of pancreatic ALES.

Currently, no consensus guidelines for the treatment of ALES exist. Previous studies have utilized a combination approach that typically starts with surgery to achieve negative margins, followed by chemotherapy and external beam radiation therapy [16,23]. One study performed neoadjuvant chemotherapy prior to surgery [16]. ALES is typically treated with the Ewing Sarcoma chemotherapy protocol. Different chemotherapy treatment regimens have been used and include: (1) Alternating combination of vincristine,

doxorubicin, and cyclophosphamide with ifosfamide and etoposide (CAV/IE, the most common regimen), (2) Doxorubicin monotherapy, (3) Carboplatin and etoposide combination therapy, and (4) Vincristine, cyclophosphamide, and actinomycin D combination therapy [15,16,18]. Post-treatment monitoring typically consists of whole-body CT ± PET scan [9,16]. Based on the limited available follow up data, ALES treatment outcomes appear to be similar to or slightly better than traditional Ewing Sarcoma with an estimated one year survival is 92% ± 7% for ALES [18,20].

In conclusion, we present a unique case of ALES of the thyroid that was diagnosed incidentally in a patient with acute right upper quadrant abdominal pain. ALES represents a distinct disease with overlapping features of carcinoma and Ewing's sarcoma. Further studies are needed to establish consensus diagnostic and treatment guidelines and optimize patient outcomes.

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