Case report

Triple whammy: a rare case of epithelioid hemangioendothelioma with synchronous angiomyomatous hamartoma complicated by *Actinomyces meyeri*

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Abstract

Epithelioid hemangioendothelioma is a rare vascular malignancy that originates from vascular endothelial or pre-endothelial cells and is composed of epithelioid or histiocytoid cells. This malignancy has an incidence of approximately one per one million individuals and can occur in various regions of the body including the lungs, liver, bones, and soft tissues. The behavior of this cancer can range from indolent to aggressive and diagnosis and treatment are often delayed due to variable presentations and lack of established treatment guidelines. Here we present the case of a 27-year-old Hispanic male that presented with right groin pain, abdominal pain, and a fifty-pound weight loss over one year. The patient had a complex hospital course during which he was found to have an angiomyomatous hamartoma of his right groin area, postsurgical right inguinal wound infection with *Actinomyces meyeri*, and epithelioid hemangioendothelioma distal to the right iliac bifurcation. The patient is currently pending further imaging studies to evaluate candidacy for surgical resection and following with oncology for chemotherapeutic options.

Keywords: *epithelioid hemangioendothelioma; angiomyomatous hamartoma; wound infection; Actinomyces meyeri*

Introduction

Epithelioid hemangioendothelioma (EHE) is a rare vascular malignancy originating from vascular endothelial or pre-endothelial cells. This malignancy has no gender or age predilection and has an incidence of approximately one per one million individuals [1]. It tends to manifest in the lungs, liver, bones, and soft tissues but has no regional preference [1].

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The behavior of this cancer ranges from indolent to aggressive and diagnosis and treatment are often delayed due to inconsistent presentations and lack of treatment guidelines [2]. To date, there are no known hereditary or environmental risk factors associated with this malignancy and it is often discovered incidentally on imaging [3]. Here we present the case of a 27-year-old male diagnosed with this uncommon sarcoma subtype.

Case report

A 27-year-old Hispanic male with no significant medical history presented to the emergency department with a one-year history of worsening right groin pain and swelling. The patient endorsed associated abdominal pain

with food consumption, loss of appetite, and a fifty-pound weight loss during this time. He reported that he had previously had three right inguinal lymph nodes removed at an outside hospital to determine the cause of his groin pain. However, the biopsies proved negative and he never completed the rest of his workup. On physical examination, the patient had mild abdominal tenderness in all four quadrants, a grossly enlarged right inguinal region, and non-pitting edema of the right lower extremity.

Computed Tomography (CT) of the abdomen and pelvis revealed an ill-defined, hypodense calcium containing lesion measuring 1.9 x 2.1 cm distal to the right iliac bifurcation causing moderate right hydroureteronephrosis (Figure 1). It also illustrated para-aortic lymphadenopathy, a cystic right inguinal lesion, and chronic occlusion of the infrarenal inferior vena cava (IVC). Venous Doppler ultrasound of the right lower extremity revealed no deep venous thrombosis, but did show an indeterminate 7.4 cm multiseptated cystic structure in the right groin. Scrotal ultrasound proved unremarkable. CT urogram was performed due to hydroureteronephrosis and demonstrated a filling defect in the right distal ureter concerning for an obstructing urothelial lesion. It also revealed right iliopsoas myositis with stranding in the adjacent retroperitoneum and soft tissue wall thickening along the right pelvic sidewall. The differential diagnosis for this patient based on his imaging findings included malignancy such as lymphoma, infection, particularly fungal, and autoimmune etiologies such as retroperitoneal fibrosis (RPF).

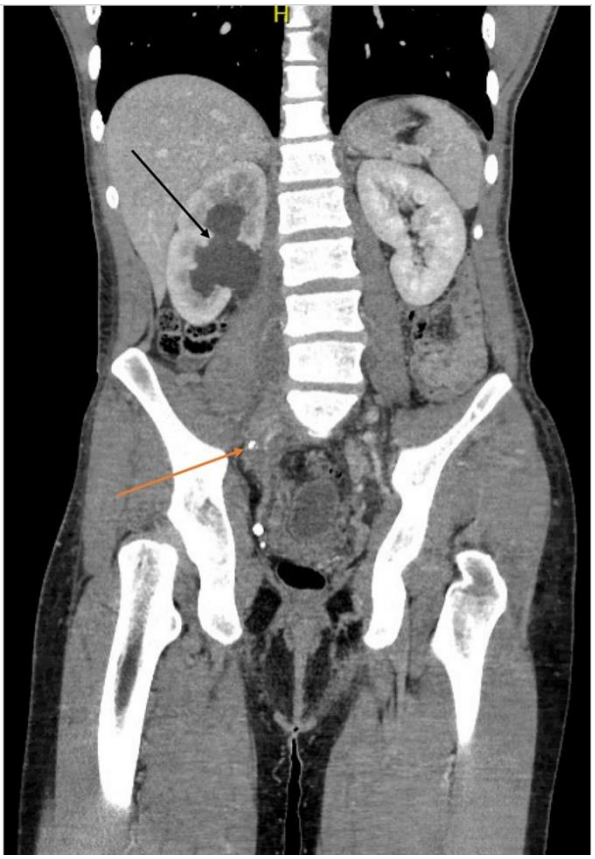

Fig. 1. Computed Tomography of the abdomen and pelvis - coronal view. Black arrow pointing to moderate right hydroureteronephrosis. Red arrow pointing to calcium containing lesion measuring 1.9 x 2.1 cm

Multiple specialties were consulted for assistance in working up this patient's complex imaging findings. Interventional radiology (IR) performed an aspiration of the patient's right groin lesion which revealed a few lymphocytes and fibrin, but no malignant cells. The results were consistent with a lymphocele which was attributed to the patient's prior inguinal lymph

nodes resection. IR also performed a CT-guided fine needle aspiration of the ill-defined retroperitoneal mass and sent the sample for pathology. However, the sample had to be sent to Mayo clinic for specialized staining. Vascular surgery performed an intravascular ultrasound and found significant narrowing of the distal IVC, right common iliac vein, and right common femoral vein for which they placed a self-expanding stent and started the patient on daily aspirin and clopidogrel. The surgeons also excised the right groin cystic mass and sent it for pathology which later resulted as a benign angiomyomatous hamartoma (Figure 2). The patient's postoperative course was complicated by development of a right groin hematoma that required evacuation and wound vacuum-assisted closure. Wound cultures obtained during the procedure resulted in growth of *Actinomyces meyeri* for which the patient was started on penicillin G IV 20 million units daily for six weeks followed by oral amoxicillin 1 g three times daily for six months.

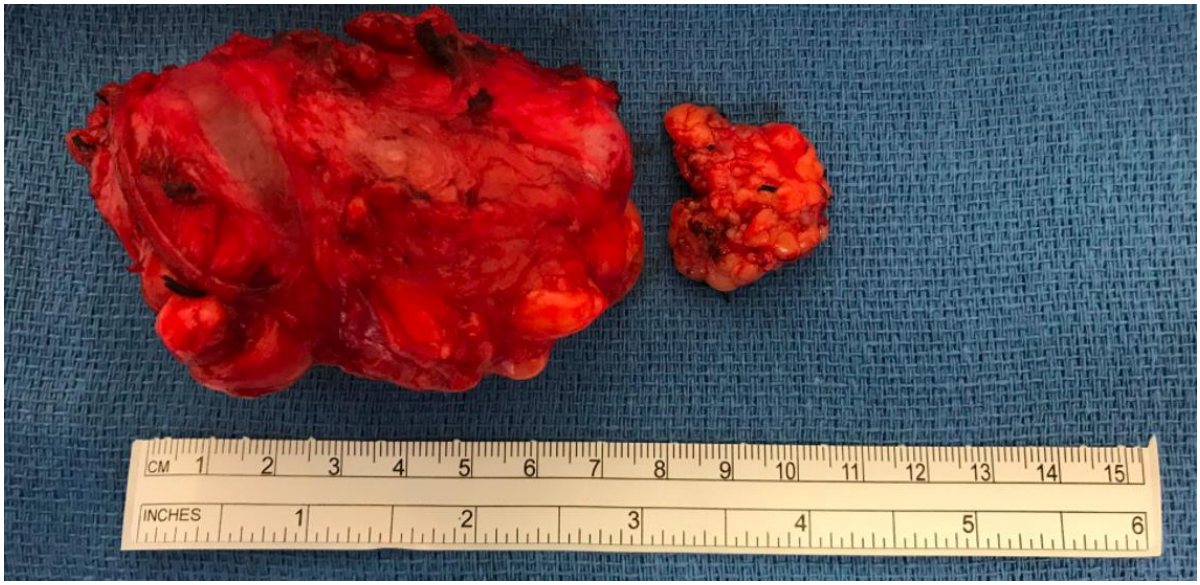

Fig. 2. Angiomyomatous hamartoma measuring 10 x 5 x 5 cm, excised from right groin

Urology was consulted for the abnormal urogram findings and recommended outpatient ureteral biopsy and management of the hydroureteronephrosis due to the patient's normal renal function and concern for retroperitoneal fibrosis surrounding the right ureter. Rheumatology recommended checking basic autoimmune labs which revealed negative antinuclear, anti-cyclic citrullinated peptides, and rheumatoid factor antibodies, but elevated IgG2 to 689 mg/dl and IgG4 to 224 mg/dl. The patient was started on a prednisone taper at 1 mg/kg daily for possible IgG4-related retroperitoneal fibrosis after his infectious workup including: human immunodeficiency virus testing, blood cultures, urine cultures, and fungal cultures proved unremarkable.

By this time, the patient's retroperitoneal biopsy results returned from Mayo clinic as an epithelioid hemangioendothelioma that was positive for the markers: cluster of differentiation 31 (CD31), erythroblast transformation-specific-related gene (ERG), friend leukemia integration 1 transcription factor (FLI1), calmodulin-binding transcription activator 1 (CAMTA1), and cluster of differentiation 56 (CD56) (Figure 3). The patient is currently pending a positron emission tomography scan to determine if the tumor will be amenable to surgical resection and it is working with oncology to determine what chemotherapy options are available.

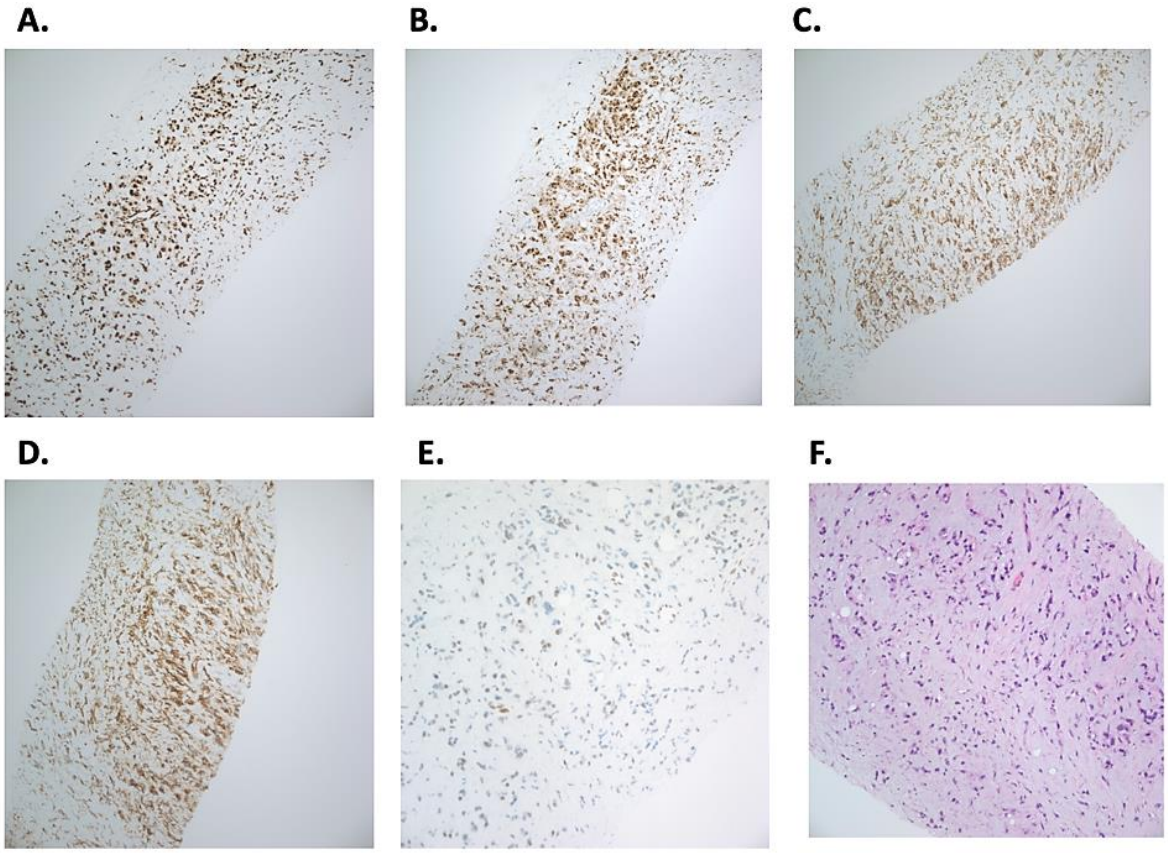

Fig. 3. Immunohistochemistry stains show EHE tumor cells are positive for: **A.** vascular marker Erythroblast transformation-specific-related gene (anti-ERG antibody, x100); **B.** tumor specific marker Calmodulin-binding transcription activator 1 (anti-CAMTA1 antibody, x100); **C.** non-specific marker Cluster of differentiation 56 (anti-CD56 antibody, x100); **D.** vascular marker Cluster of differentiation 31 (anti-CD31 antibody, x100); **E.** Friend leukemia integration 1 transcription factor (anti-FLI1 antibody, x100). **F. c**ords and single cells of large endothelial cells with abundant eosinophilic cytoplasm embedded in a myxohyaline stroma (HE, x200).

Discussions

EHE is a rare vascular malignancy that affects approximately one in one million individuals. This cancer has no gender or age preference and tends to have an uncertain clinical course ranging from indolent to aggressive disease [1, 2]. There are no known risk factors for this malignancy, and it is often discovered incidentally on imaging studies performed for other reasons [3]. Diagnosis is made by characteristic histologic findings on biopsy specimens of abnormal epithelioid endothelial cells arranged into cords, strands, and aggregates in a hyaline, myxoid, chondroid, or collagenous stroma [1, 4, 5]. Tumor cells often stain positive for ERG, CD31, cluster of differentiation 34 (CD34), FLI1, podoplanin, and von Willebrand factor, while CAMTA1 and transcription factor E3 (TFE3) only stain positive in fusion gene tumors [6, 7]. The average survival time after diagnosis is highly variable and depends on whether the patient is symptomatic from the disease, location of the malignancy, and the aggressiveness of the cancer [2]. There are no established treatment guidelines for EHE. However, for localized disease, surgical management is preferred. Other treatment options include vascular embolization, vascular endothelial growth factor inhibitors such as pazopanib, and cytotoxic chemotherapy such as gemcitabine [1].

This patient's case was unique because of the broad differential diagnosis associated with his imaging and laboratory findings. He initially presented to the emergency department for right groin pain and swelling that was discovered to be an angiomyomatous hamartoma, a benign overgrowth of smooth

muscle, blood vessels, and adipocytes [8]. Although both angiomyomatous hamartoma and epithelioid hemangioendothelioma are vascular lesions, not enough data exists to determine if there is a developmental correlation between the two diseases.

Retroperitoneal fibrosis, a disorder distinguished by inflammatory and fibrous tissue within the retroperitoneum was also considered for this patient because of his hydroureteronephrosis and elevated IgG4 level. The patient was started on an empiric prednisone taper, but this was stopped after his biopsy results returned negative for fibrosis. It is important to note that although the majority of primary RPF cases are idiopathic, secondary RPF can result from infection, malignancy, and retroperitoneal hemorrhage [9].

Lastly, abdominal actinomycosis was also on the differential diagnosis due to the patient's wound culture growth of *Actinomyces meyeri* and his imaging findings of solid and cystic masses with concern for infiltrative disease [10]. However, the retroperitoneal mass biopsy result was negative for sulfur granules excluding abdominal actinomycosis as the patient's final diagnosis. Furthermore, *Actinomyces israelii* is the most common cause of abdominal actinomycosis and not *Actinomyces meyeri* [11].

Conclusions

EHE is a rare vascular malignancy of unpredictable behavior. Diagnosis is made through biopsy specimen analysis and treatment generally depends on the aggressiveness of the tumor. EHE may be mistaken for benign conditions depending on its location and appearance on imaging, making it particularly important for clinicians to have a broad differential diagnosis and a high level of suspicion when encountered. At this time, further research of the disease is necessary to establish treatment guidelines, particularly for patients with aggressive disease.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing Interest

The authors declare that they have no competing interests.

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