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CASE STUDY

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Giant thigh glomus tumor of uncertain malignant potential: Case report with pathologic–radiologic correlation

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Abstract

Introduction: Glomus tumors (GT) are rare, benign tumors that arise from glomus bodies and usually develop in digital areas. Extradigital GT are exceptional and thigh location is infrequent.

Case Report: We report a case of a GT of the thigh in a 79-year-old male patient that measured 9.5 cm in maximum size. The GT lay above the muscular fascia without infiltrating it. Internal hypervascularity was seen by spectral Doppler ultrasound. Magnetic resonance image showed a heterogeneous mass with hyperintense and hypointense components and internal lobes with liquid–liquid levels. Histopathology revealed a monotonous round-cell proliferation with central nuclei without atypia or mitotic figures, around small-caliber vessels. These cells expressed smooth muscle actin and pericellular collagen IV. GT of uncertain malignant potential was diagnosed. The mass was completely removed. The patient did not experience local relapse nor distant metastasis.

Conclusion: GT are rare soft tissue tumors whose diagnosis of unusual giant masses in uncommon locations may be delayed and misdiagnosed given the low suspicion.

KEYWORDS
extradigital glomus tumor, giant tumor, glomus tumor, glomus tumor of uncertain malignant potential

1 | INTRODUCTION

Glomus tumors (GT) were first described by Wood in 1812.[1] They are thought to arise from the neuromyoarterial cutaneous bodies (glomus bodies [GB]).[2] GT account for fewer than 2% of soft tissue tumors.[3] The great majority are small (<1 cm) nodules that develop in the dermis or subcutis of the fingers and toes.[4] Extradigital GT (eGT) may develop in any anatomical area.[5]

Ultrasound appearance of GT consists in a circumscribed hypoechoic oval nodule located in the subcutaneous layer and oriented horizontally. Spectral Doppler shows both venous and arterial intralesional flow. In some cases, a "vascular stalk sign" in correlation with the presence of prominent vascular flow connecting the lesion to the adjacent soft tissue may be seen.[6] The appearance on magnetic resonance image (MRI) consists of a T2-weighted hyperintense lesion with avid enhancement as a result of its high vascularity. It usually shows low signal in T1-weighted images (WI) unless there is intralesional hemorrhage, in which case it shows high signal foci.[7]

Most cases are benign lesions composed of modified smooth muscle cells (glomus cells).[4] These cells are usually rounded with central nuclei, but may be spindled or present oncocytic changes.[3] Glomus cells show immunohistochemical positivity for smooth muscle actin (SMA), muscle specific actin, calponin, h-caldesmon and collagen IV[4] and are negative for S100 and cytokeratins.[4] Malignant GT are exceptional and highly aggressive.[4] Cases that do not completely fulfill the criteria for malignancy are called GT of uncertain malignant potential (GT-UMP).[8]

The objective of this article is to present clinical, radiological, histopathological features, and surgical management of this rare tumor of soft tissues in a case with an unusual size and location.

2 | CASE REPORT

2.1 | Clinical findings

A 79-year-old male was referred to our hospital for evaluation of a lump in his left thigh. It had been noticed 4 years ago and had been enlarging progressively during last months. He denied any recent local trauma. The only relevant personal medical antecedent was a transient ischemic cerebral accident with no sequelae. Physical examination revealed a painful, multilobulated and barely movable mass in his left thigh. Full hip and knee range of motion were maintained.

Computerized tomography (CT)-guided biopsy of the lesion was performed with a histopathological diagnosis suggestive of GT-UMP. Patient underwent a wide resection of the mass, including the skin and surrounding soft tissue.

2.2 | Radiological findings

The ultrasound examination of the anterior aspect of the left distal thigh showed a large multilobulated, well-defined, heterogeneous mass with echogenic and anechoic areas (Figure 1A). The tumor measured 7 cm anteroposteriorly, 7 cm mediolaterally, and 8 cm in craniocaudal dimension. Spectral Doppler ultrasound showed internal hypervascularity in its inferior half (Figure 1B).

MRI evaluation showed a heterogeneous lesion with hyperintense and hypointense elements and internal lobes with liquid–liquid levels, representing areas of blood of variable age alternating with

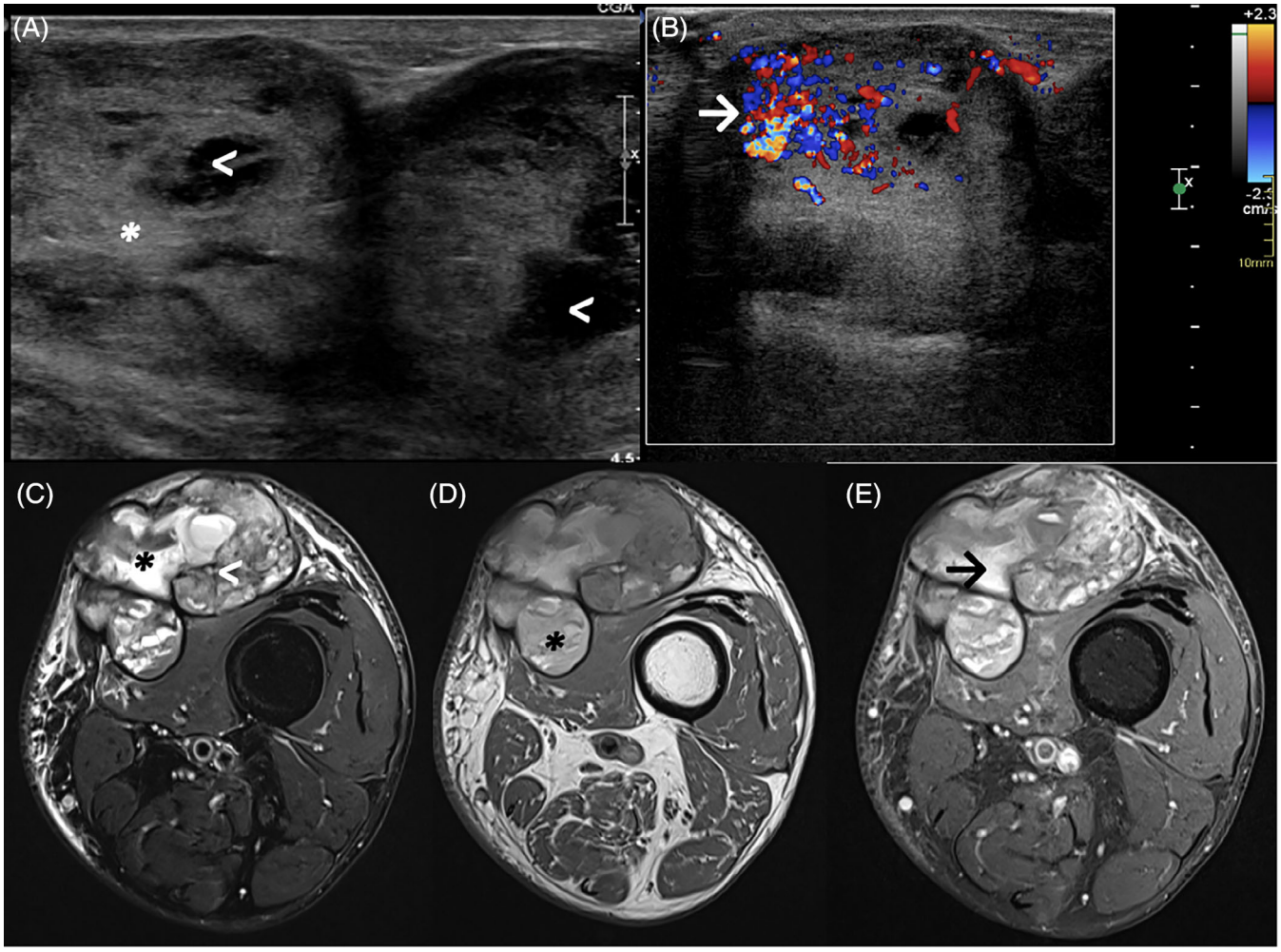

FIGURE 1 (A) B-mode ultrasound image: large multilobulated, well-defined and heterogeneous lesion with echogenic (*) and anechoic (<) areas. (B) Color Doppler ultrasound: internal hypervascularity in its inferior half (→). (C) Axial T2 fat sat-weighted MRI: heterogeneous lesion with hyperintense (*) and hypointense (<) elements, representing areas of blood of variable age alternating with solid components. Hypointense peripheral rim (hemosiderin deposits). (D) Axial T1-weighted MRI: high intensity inside the lesion consistent with blood products (*). Hypointense peripheral rim (hemosiderin deposits). (E) Axial post contrast MRI image: enhancement of the solid component in its inferior pole (→).

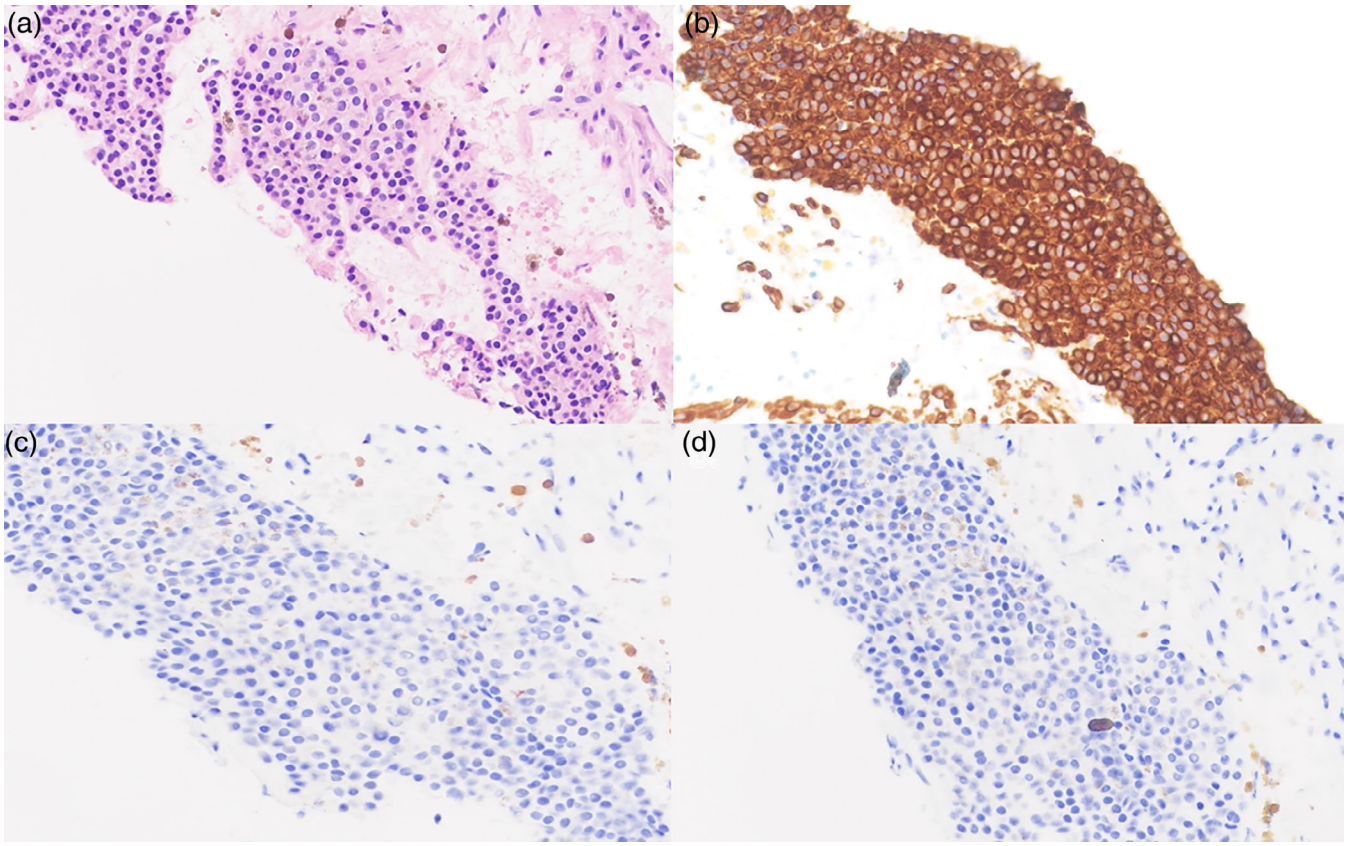

FIGURE 2 (A) Round and well-defined cells with eosinophilic cytoplasm and central oval nuclei (200, H&E). (B) Diffuse positivity (×200, SMA). (C) Negative staining (×200, cytokeratin AE1/AE3). (D) Negative staining (×200, synaptophysin).

solid components (Figure 1C). In the T1 WI (Figure 1D) the areas of high intensity inside the lesion were consistent with blood products. After the administration of paramagnetic contrast (Figure 1E), the solid component in the inferior pole of the lesion showed avid enhancement. The lesion was encapsulated with a surrounding rim of low T1 and T2 signals.

Thorax CT showed no distant lesions.

2.3 | Histopathologic and molecular features

The biopsy specimen consisted of a monotonous proliferation of round cells with well-defined margins, eosinophilic cytoplasm, and central oval nuclei with heterogeneous chromatin (Figure 2A). Immunohistochemically, SMA (clone 1A4, ready to use [RTU]; Agilent-Dako) (Figure 2B) and vimentin (clone V9, RTU; Agilent-Dako) were diffusely positive. S100 (polyclonal, RTU; Agilent-Dako), desmin (clone D33, RTU; Agilent-Dako), cytokeratins (clone AE1/AE3, RTU; Agilent-Dako) (Figure 2C) and synaptophysin (clone DAK-SYNAP, RTU; Agilent-Dako) (Figure 2D) were negative. Cell proliferation index (Ki67 [clone MIB-1, RTU; Agilent-Dako]) was less than 1% (Figure 2E).

The surgical specimen was grossly composed of two ovoid, pseudoencapsulated, well-circumscribed nodules that measured 9.5 × 7.5 × 4.5 cm and 2 × 1 × 1 cm, respectively (Figure 3A). Both were located in the subcutaneous tissues above the muscular fascia, without infiltrating it. On sectioning there were predominantly solid areas intermixed with bloody spaces.

Twelve tumoral sections of different areas were included for microscopic examination. Microscopically, the nodules were formed of cell nests without atypia surrounding small-caliber vessels (Figure 3B). Nests had the same cellular composition as described in the diagnostic biopsy. Infiltrative growth pattern was not seen. No mitotic figures nor necrosis were observed. No lymphovascular nor perineural infiltration were identified. SMA (Figure 3C) and pericellular collagen IV (Figure 3D) were diffusely positive. BRAF (clone DAK-BRAF V600E, RTU; Agilent-Dako) was not immunohistochemically expressed. Surgical margins were not affected.

2.4 | Clinical evolution

No early postoperative complications were developed. Thigh MRI and thorax-abdomen-pelvis CT performed at 3 and 6 months after surgery showed no local recurrence or extension disease. Five years after tumoral resection the patient is free of disease.

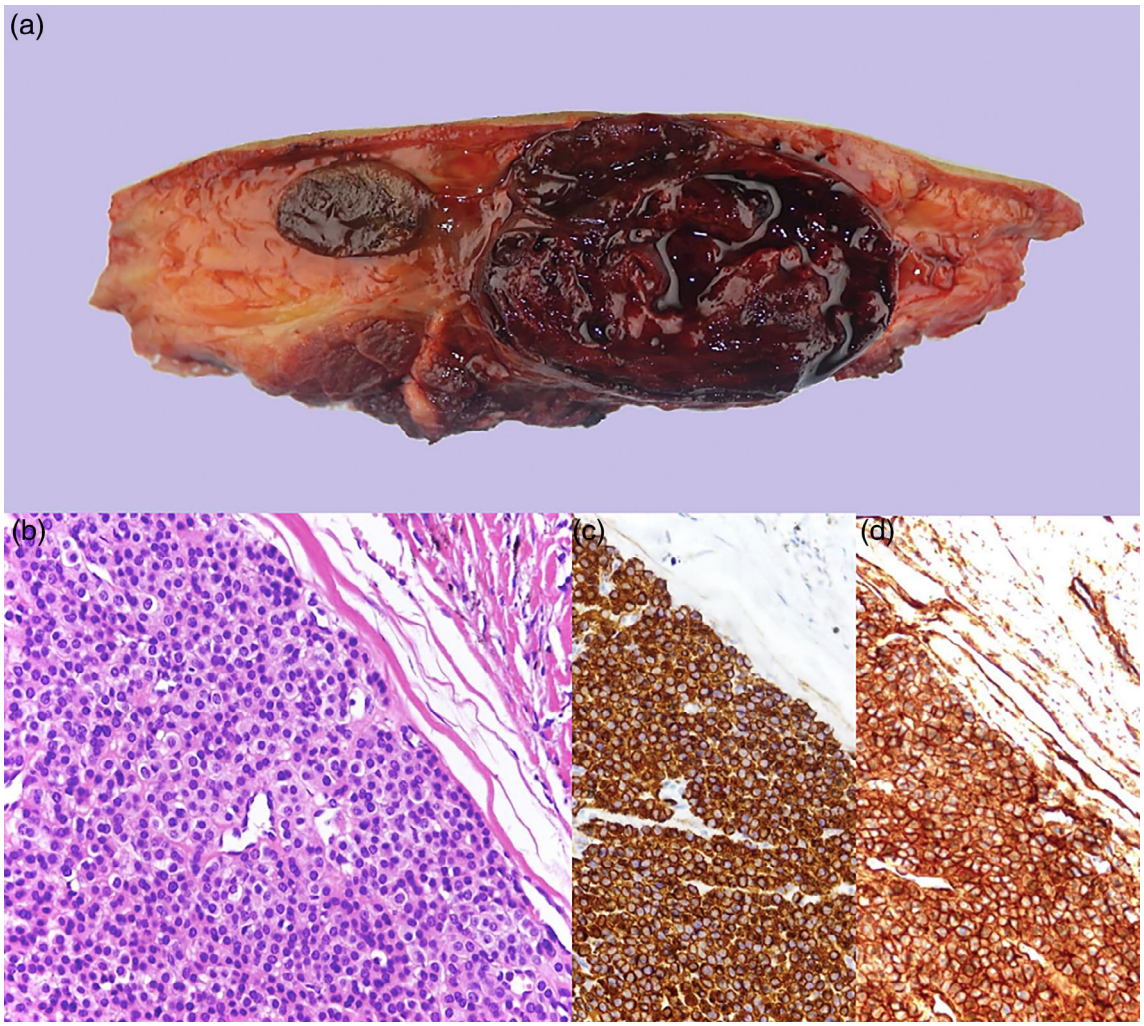

FIGURE 3 (A) Middle section of surgical specimen: well-circumscribed predominantly solid nodules with bloody areas. (B) Monotonous cell proliferation without atypia around capillary-sized vessels (×200, H&E). (C) Diffuse positive staining (×200, SMA). (D) Diffuse pericellular positive staining (×200, collagen IV).

3 | DISCUSSION

GT are very rare soft tissue tumors that originate from GB, whose principal functions are temperature and vascular tone regulation.[4] The classic clinical triad of pain, tenderness and cold hypersensitivity[5] was not present in our patient. Schiefer et al[9] reported a series of 56 patients with eGT. Eighty-six percent of them presented pain and localized tenderness but only 2% developed cold hypersensitivity. As a result of the location, size and progressive growth of the mass during last months, sarcoma was suspected in our patient. GB are densely found in acral locations, especially in subungual region, fingers and toes.[10] eGT are exceptional and may occur anywhere.[4] The location in the thigh is unfrequent.[5] Thirty-three cases of thigh GT have been reported in English literature.[5,6,8–21] In a series of 138 GT reported by Mravic et al,[22] 11.6% cases were located in legs, but there is not specified thigh location. GT are usually small lesions (<1 cm)[4] but cases over 10 cm have been reported in ankle and paraspinal area by Folpe et al.[8] Other thigh GT reported cases were small size lesions (between 0.5 and 3 cm).[5,12,14,15,17–19] In these cases, a wide sample of different tumoral areas must be performed.

Our case did not show aggressive radiological signs despite its size and the complexity of its internal structure. The presence of liquid–liquid levels and the deposition of hemosiderin as a result of continuous hemorrhagic phenomena suggested a tumor of vascular origin. The main differential diagnosis included low- to intermediate-grade vascular tumors such as hemangioendothelioma or a higher-grade vascular tumor (angiosarcoma). These tumors share imaging features with our case. These features are relatively non-specific and include an enhancing soft tissue mass, with high signal intensity on T2 WI and may include foci of high signal intensity on T1 WI, indicating hemorrhage foci. However, the most diagnostic finding for vascular tumors is the presence of high-flow serpentine vessels that show low signal intensity on both T1 and T2 weighted images,[23] which were not present in our patient. Another useful clue to differ our case from angiosarcoma is the invasiveness of the latter into surrounding tissues, although this is not present in every case.[24] Other radiological

differential diagnosis should consider undifferentiated pleomorphic sarcoma (UPS). UPS can show calcification or ossification within the tumor in 5%–20% of cases, and bone erosion or infiltration is common.[25] To conclude, the radiological features between these entities and our case are non-specific and overlap. As a result of the concern for a malignant lesion a biopsy is needed for an accurate diagnosis.

Folpe et al[8] proposed a classification for GT. Malignant GT should be diagnosed in the presence of atypical mitotic figures or marked atypia and mitotic activity (>5/50 high power fields [hpf]).[8] GT-UMP diagnosis is reserved in cases with superficial location and high mitotic activity (>5/50 hpf) or large size (>2 cm) and/or deep location.[4] Our case consisted in a 11.5 cm well-defined mass in subcutaneous tissues without fascial infiltration. Microscopically it was composed of non-atypical cells without mitosis or necrosis. Based on these criteria, GT-UMP was diagnosed in our patient.

The main histopathological differential diagnosis of benign GT is mainly with myopericytomas and myofibromas. Typical GT are composed of round cells with well-demarcated membranes while myofibromas and myopericytomas contain less-rounded cells with ill-defined borders.[2] Some non-typical GT may present spindled morphology and hemangiopericytoma-like vessels overlapping with myofibroma.[2] In these cases, classical GT histopathology should be carefully searched. Angioleiomyomas are composed of fusiform smooth muscle cells with diffusely positivity for SMA in bundles or whorls surrounding numerous vascular channels.[26] Hemangiomas are usually composed of lobules of capillary-sized vessels lined by a single layer of flattened endothelial cells.[2] Benign GT are easily distinguishable from malignant vascular tumors such as angiosarcoma because these last present marked nuclear atypia and an infiltrative pattern.[4] Benign adnexal tumors (nodular hidradenoma or eccrine spiradenoma) may present difficult histopathologic distinction from GT, especially between GT with inconspicuous vascular channels and solid cellular hidradenomas. Adnexal tumors present variable epithelial or sebaceous differentiation, positivity for cytokeratins and CEA, and negativity for SMA.[2] Paragangliomas present a prominent Zellballen growth pattern, positivity for chromogranin and synaptophisin, and negativity for SMA.[3] Neuroendocrine tumors contain salt and pepper chromatin, are positive for cytokeratins, chromogranin and synaptophysin, and negative for SMA.[3] *BRAF* mutation has been proposed to be associated with malignant features.[27] Our case do not express BRAF immunohistochemically.

Small GT are cured by complete resection but may recur locally within days to weeks if are not totally removed.[2] The recurrence rate of eGT after resection is reported in up to 10% of the cases.[2] The behavior of GT-UMP is unpredictable but most follow a benign clinical course,[3] as our patient did. A minority of GT-UMP may present distant metastases, especially to the lungs.[3] Although our case did not show malignant histopathological features, it presented some unusual clinical characteristics, so systemic follow-up was decided in the committee.

4 | CONCLUSION

eGT should be suspected in cases of small painful nodules with localized tenderness and radiologic images suggestive of vascular lesions. The absence of the typical clinical symptoms, the unusual location on the thigh and the unusual size of our GT delayed the diagnosis as a result of the low level of suspicion. Knowing this unusual presentation is important to keep in mind GT in the differential diagnosis of similar cases.

AUTHOR CONTRIBUTIONS

Conception and design of the study and acquisition and analysis of data: EM Pena-Burgos and JJ Pozo-Kreilinger. Drafting the manuscript: EM Pena-Burgos, G Serra-Del Carpio, M Tapia-Viñe, EJ Ortiz-Cruz, and JJ Pozo-Kreilinger. Radiology images: G Serra-Del Carpio and M Tapia-Viñe. Pathology figures: EM Pena-Burgos and JJ Pozo-Kreilinger.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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