Wünderlich Syndrome From a Malignant Epithelioid Angiomyolipoma

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INTRODUCTION

Angiomyolipoma of the kidney has classically been considered as a tumor of the connective tissue composed of fat, vascular tissue, and smooth muscle. In most cases, it is a tumor with benign behavior that may appear sporadically or associated with tuberous sclerosis syndrome. Macroscopically, these tumors are greyish yellow in color, and under an optical microscope, they are characterised by presenting the three components described. In recent years, several authors have published cases of epithelioid angiomyolipomas characterized by a minimal presence of fat in the tumor, positive for the melanoma-specific antigen, HMB-45,[(1)] and on occasion, positive for desmin, melan-A, and others.[(2,3)] Computed axial tomography and nuclear magnetic resonance studies hardly differentiate epithelioid angiomyolipomas from renal cell carcinoma.[(3)] We present a case of malignant epithelioid angiomyolipoma in a woman with no tuberous sclerosis, the debut of which was spontaneous retroperitoneal hemorrhage causing hypovolemic shock that required left radical nephrectomy.

CASE REPORT

A woman aged 47 years old with no medical background of interest presented to the accident and emergency service complaining of sudden spontaneous pain in the left renal fossa and left abdomen, accompanied by nausea and vomiting. During clinical examination, blood pressure of 120/65 mm Hg and a heart rate of 90 per minute were recorded, and the pain was localized in the left half of the abdomen and left renal fossa, with no signs of peritoneal irritation. On blood tests, hemoglobin was 9.5 g/dL; hematocrit, 29%; platelet count, 230×10^9/L; and hematite, 3 640 000/μL. Urine sediment was normal. The most significant finding of a single abdominal radiography was the lack of vision of the left psoas line. Treatment was begun with serum therapy, analgesia, and clinical observation.

One hour later, the patient presented arterial hypotension (90/50 mm Hg), tachycardia (130 per minute), peripheral hypoperfusion, and a generally poor condition, which was controlled by administering 1000 mL of crystalloids. Abdominopelvic computed axial tomography revealed retroperitoneal hematoma from the left subdiaphragmatic region to the left pelvic region, with

morphological changes in the upper pole of the left kidney (Figure 1). A second blood test showed a decrease in the hematite count to 2 730 000/μL; hemoglobin, to 7 g/dL; and hematocrit, to 21%. Three hematite units were transfused.

Left lumbotomy was performed, extracting a large quantity of serohematic clots and liquid, with hemorrhage persisting from the upper half of the left kidney that could not be controlled, making it necessary to perform a pedicle ligature and left nephrectomy. Postoperatively, the patient progressed well. Control clinical studies revealed only an increase in the tumor marker CA125 (70.45 UI/mL; reference level, < 35 UI/mL), with all other analytical parameters within the reference ranges (hematite count, 4100000/μL; hemoglobin, 13.4 g/dL; hematocrit, 37%; urea, 25.4 mg/dL; creatinine, 0.8 mg/dL; and prolactin, 22.9 ng/mL).

Histology of the sample revealed that the tumor was composed of thick-walled smooth-muscled blood vessels, most notably in the perivascular areas, mixed with mature fatty tissue (Figure 2). Sandwiched between these two components, solid areas of large mononuclear or multinuclear areas were observed, with a pleomorphic hyperchromatic nucleus, prominent nucleolus, and abundant cytoplasm, clear in most cases, and eosinophilic in others. High atypical mitotic activity and necrotic areas were also seen, showing evident proliferative activity and malignance. Immunohistochemical study showed reactivity in the epithelioid cells for HMB-45, melan-A, and smooth-muscle actin and desmin, with a greatly

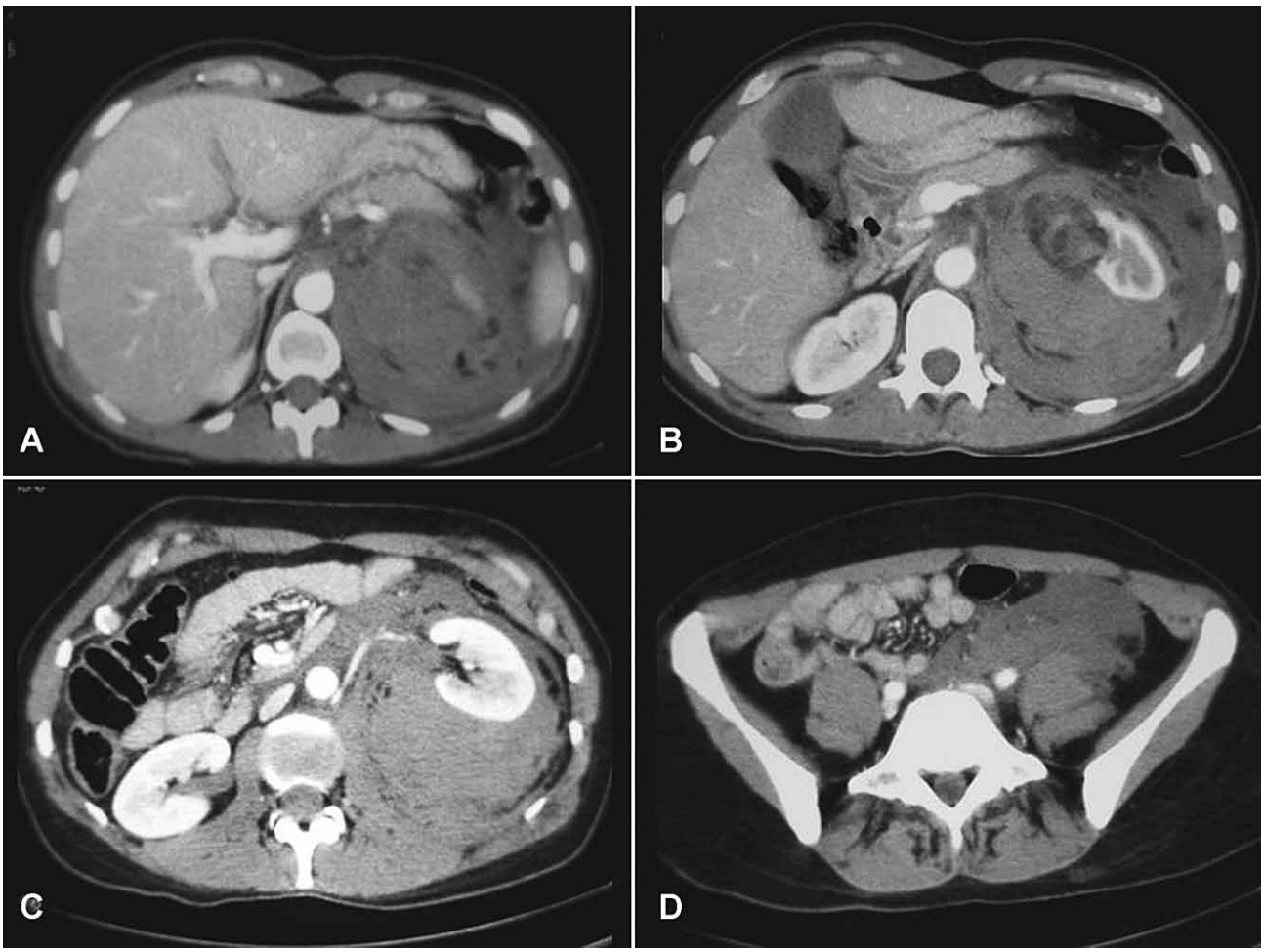

Figure 1. A, Presence of hematoma in the left subdiaphragmatic region. **B**, Nodule of fatty density, 4 × 3 × 4.5 cm, at the upper pole of the left kidney, suggesting angiomyolipoma, with major perirenal hematoma displacing forward towards the pancreas, stomach, spleen, and left kidney. Hypodense image suggests cyst of the liver in segment 6. **C,** Retroperitoneal hematoma displacing left kidney and pancreas with circumaortic left kidney vein. **D,** Image of the same retroperitoneal hematoma extending towards the pelvis with free liquid in the Douglas space.

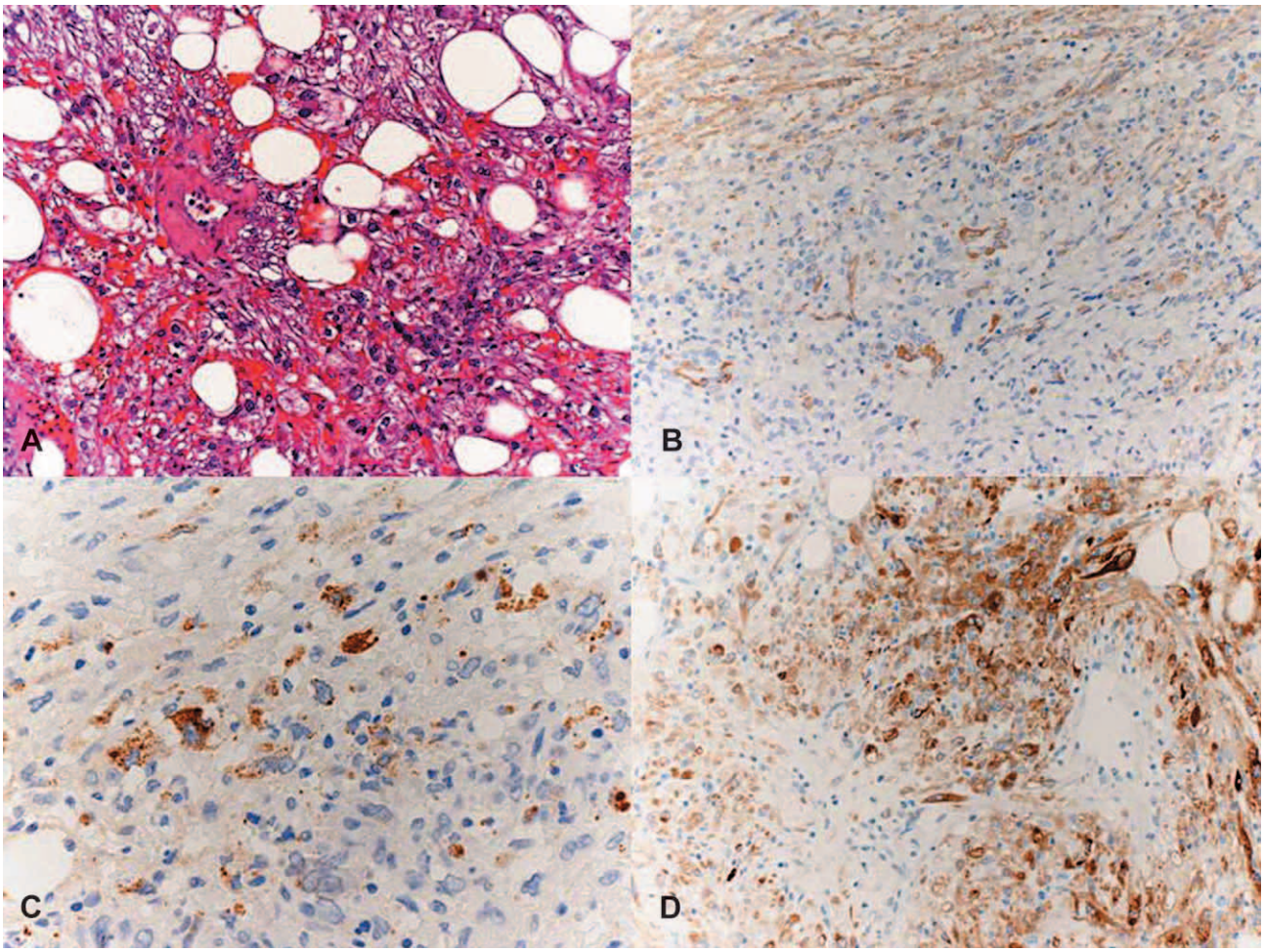

Figure 2. A, Staining by hematoxylin-eosin shows thick-walled blood vessels, smooth muscle, and mature fatty tissue with atypical cells of epithelioid appearance. **B,** Immunohistochemistry with reactivity for smooth-muscle actin. **C,** Immunohistochemistry with focal reactivity for HMB-45. **D,** Immunohistochemistry with focal reactivity for melan-A.

increased cell proliferation index (Ki67).

Twelve months after the treatment, the patient was free of disease.

DISCUSSION

Owing to the difficulty of differential diagnosis of renal angiomyolipoma from other tumoral entities of the kidney, the HMB-45 positivity in renal angiomyolipomas was first proposed in 1991, favoring its histological and immunohistochemical differentiation.[1] In 1947, Apitz described perivascular epithelioid cells for the first time as abnormal myoblasts inside angiomyolipomas.[4] Thereafter, these cells began to be described more accurately, proving positive for HMB-45, desmin, Melan-A, HMSA-1, and other markers, leading to the proposal of a new tumoral entity called perivascular epithelioid cell tumor (namely, PEComa).[5] The epithelioid variety of angiomyolipoma has been defined histologically as the presence of pure epithelioid cells with positive melanogenesis markers, without the presence of adipocytes or vascular tissue. However, some classical angiomyolipomas present epithelioid cells with an atypical component, a high proliferative index and focal necrosis indicating a malign tumoral process that may be considered as epithelioid angiomyolipoma.[5] Genetic studies have been performed confirming the existence of allelic disorders in chromosome 16p (gene *TSC2*), which may alter the route rev/mTOR/p70S6K and are present in PEComas and angiomyolipoma.[5,6] The expression of such growth factors as CD117 or, as in our case, Ki67 has been observed, as well as

disorders in the tumor-suppressant gene *P53*.[7,8] In one published case, the presence of very high prolactin levels was seen, which returned to normal after the tumor was removed.[2]

It is far from easy to carry out an epithelioid angiomyolipoma diagnosis using imaging techniques, particularly when it comes to differentiating it from renal cell carcinoma. For this reason, radical nephrectomy is usually indicated after computed axial tomography or nuclear magnetic resonance studies. The main treatment applied in such patients is usually radical nephrectomy, with adjuvant therapy in these cases being the subject of some controversy, although these tumors have been described as being chemosensitive to doxorubicin, d-carbacin, ifosfamide, cyclophosphamide, and cisplatin.[3] Cases have been described of metastasis extending into the liver, bone, and retroperitoneum either during diagnosis or after a period of monitoring,[9] making it vitally important to establish a clear adjuvant therapy for this patient group.

The incidence of epithelioid angiomyolipoma is thought to be underestimated owing to the difficulties to date differentiating it in diagnosis from liver cell carcinoma, with many diagnoses given as liver cell carcinoma actually being epithelioid angiomyolipoma.[10] We consider the exploration of preoperative differential diagnosis of this pathology using imaging techniques, enabling us to apply a better therapeutic strategy. Great progress has been made in the histological and immunohistochemical fields, making it easier for us to arrive at microscopic diagnosis, although we still need further studies to allow the etiology and etiological factors involved, adjuvant therapy and short-term and long-term prognosis for these patients to be determined.

CONFLICT OF INTEREST

None declared.

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