Bilateral angiomyolipoma, tuberous sclerosis, and pregnancy


RESUMEN
El angiomiolipoma es un tumor renal benigno relativamente infrecuente, con incidencia aumentada en pacientes con esclerosis tuberosa. Éste es un desorden autosómico dominante, caracterizado por lesiones hamartomatosas en múltiples órganos y frecuentemente afectando el riñón. El estado de gravidez es una condición que puede agudizar la sintomatología ante tumores renales previamente silentes, por lo que su diagnóstico y tratamiento se torna más complejo en el embarazo. Presentamos el caso de una mujer de 25 años, con diagnóstico previo de esclerosis tuberosa, que en la octava semana de gestación se manifestó con hematuria anemizante, identificándose angiomiolipoma renal bilateral, que ante falla al tratamiento expectante, se trató mediante embolización selectiva.

Palabras claves: Angiomiolipoma bilateral, esclerosis tuberosa, embarazo, México.

INTRODUCTION
Angiomyolipoma is a benign tumor that presents in 0.3% of the general population, making it relatively infrequent.

It represents 3% of solid renal tumors and is made up of mature adipose tissue, smooth muscle, and irregular blood vessels in varying proportions. Tuberous sclerosis is a neurocutaneous, dominant autosomal pathology.

ABSTRACT
Angiomyolipoma is a relatively infrequent benign renal tumor whose incidence increases in patients with tuberous sclerosis, a dominant autosomal disorder characterized by hamartomatous lesions in multiple organs, frequently affecting the kidney. Pregnancy can intensify the symptomatology of previously silent renal tumors, making their diagnosis and treatment more complex. We present the case of a 25-year-old woman with a previous diagnosis of tuberous sclerosis, who in her eighth week of pregnancy presented with anemia-causing hematuria. Bilateral renal angiomyolipoma was identified and when expectant treatment failed, she was treated with selective embolization.

Keywords: Bilateral angiomyolipoma, tuberous sclerosis, pregnancy, Mexico.
with a presentation of multiple hamartomas, involving various organs such as the brain, kidney, and lung. The most frequent renal affection in tuberous sclerosis is angiomyolipoma and renal cysts, presenting in 34 to 80% of cases.  

There is an increased risk for retroperitoneal bleeding (Wunderlich syndrome) in the pregnant patient. The association of these entities becomes a problem that is not always easy to resolve. Conservative management is sought, as well as genetic orientation for future pregnancies. Computed axial tomography and nuclear magnetic resonance (NMR) imaging enable the identification of fat inside the tumor. The latter is the imaging choice when dealing with pregnancy and an at-risk product. 

Once diagnosis is confirmed and the symptomatology is taken into account, the therapeutic focus, which can range from observation to radical nephrectomy, must be evaluated.  

**CASE PRESENTATION**

The patient is a 25-year-old woman with a past medical history of tuberous sclerosis detected at 2 years of age, characterized by convulsive crises controlled with 200 mg per day of carbamazepine, hypopigmented cutaneous lesions, and facial angiofibromas. She was in her 8th week of pregnancy from the date of her last menstruation, which was confirmed by obstetric ultrasound.

The patient was referred to the urology service from the zone general hospital due to total gross hematuria that was clot-forming, nonpainful, and causing anemia. Her referral included an ultrasound study showing a bilateral kidney tumor (Figures 1 to 3). It characteristically revealed a hyperechoic image in the left lower pole and renal hilum and in the right upper pole. A NMR image was taken (Figures 4 to 6) which provided the same information as the ultrasound study, with no evidence of retroperitoneal bleeding, and so expectant management was initially decided upon.

Physical examination only detailed the cutaneous lesions as neoformations on the surface of the thorax and extremities, as well as hypopigmented lesions on the abdomen and extremities. The 20 F 3-way Foley transurethral catheter showed a hematic hue (+). Laboratory parameters of full blood count upon admittance were: leukocytes 12,000, hemoglobin 8.5g/dL, platelets 368,000, glucose 78mg/dL, urea 30mg/dL, BUN 14mg/dL, sodium 139, potassium 4.3, and chloride 109.

One day later, hemoglobin was 7.6 g and the rest of the laboratory tests were normal. Four units of packed red blood cells were transfused.

The patient underwent diagnostic cystoscopy which showed a coagulate that took up approximately 70% of the bladder, two orthotopic ureteral meatuses, and marked bleeding from the right ureteral meatus. Selective arterial embolization (renal) with purified porcine skin gelatin (Gelfoam®) was carried out and hematuria subsided.

During her hospital stay, the patient presented with symptoms of cholestasis that manifested with jaundice and a total bilirubin elevation of 17.25, with direct bilirubin of 13.9, and indirect of 3.35, glutamic pyruvic transaminase (GPT) 87, glutamic-oxaloacetic transaminase (GOT) 58, alkaline phosphatase 128, and lactate dehydrogenase (LDH) 2,608. After digestive surgery service evaluation and a biliary tract ultrasound, surgical pathology was ruled out. The gastroenterology service suggested cholecystitis after excluding a viral, medical, or infectious condition. Four days after having been elevated, total bilirubin values went down to 2.05, direct bilirubin was 1.8, indirect bilirubin was 0.25, GPT was 54, and GOT was 38.
The patient was under surveillance in the hospital for two more days and did not present with any other complications and was released two days later. She was asymptomatic, diuresis was normal, and control pelvic ultrasound was normal.

**DISCUSSION**

Angiomyolipomas are uncommon renal tumors that were first described by Fischer in 1911, but it was Morgan et al. who in 1951 gave them the name, angiomyolipoma. 2,5-7 It is a tumor that from the histologic perspective is made up of benign mesenchymal tissue classified as hamartomas and, in varying degrees, is composed of mature adipose tissue, smooth muscle fibers, and blood vessels with irregular thickness and no elastic fibers. 2 This tumor can be found in 0.3% of autopsies and in 0.13% of incidental findings in the population undergoing ultrasound studies. 7

Sporadic angiomyolipomas tend to present more often in women than in men, with a 2:1 ratio. They rarely present before puberty and the mean age at which they appear is 30 years. They are inadvertent in the majority of cases. 7

Another characteristic of angiomyolipomas is that they present with estrogen receptors in smooth muscle cells and have positive immunoreaction for HMB-45, caused by the presence of monoclonal antibodies that react specifically with the premelanosomes that are present in smooth muscle cells. 3

The importance of this reactivity is its capacity to differentiate angiomyolipoma from other tumors that are derived from connective tissue, such as liposarcoma and sarcomatoid histiocytoma, because only angiomyolipoma is reactive to HMB-45. 3

Approximately 20-30% of angiomyolipomas manifest in patients with tuberous sclerosis, and of those patients, up to 80% of the tumors are bilateral. 2,3,7

Some authors suggest that there is an obvious development of renal angiomyolipoma during pregnancy, indicating a clear hormonal influence. 2 The risk of spontaneous retroperitoneal bleeding, or the Wunderlich syndrome, also increases during pregnancy, supporting the idea of hormonal dependence, and in addition, is favored by the increase in blood volume and renal flow. 2,7

Diagnostic methods include ultrasound, computed tomography, and magnetic resonance and have produced a notable increase in the incidental diagnosis of renal masses. There are many radiographic characteristics that lead to diagnosis. However, the presence of fat in renal lesions seen with tomography excludes renal cell carcinoma diagnosis, making it necessary to consider angiomyolipoma. 2,7 In ultrasound, lesions with high echogenicity associated with posterior acoustic shadowing, such as those seen in our patient, are typical but not pathognomonic.

Renal angiomyolipoma is strongly associated with tuberous sclerosis, a dominant autosomal disease with incomplete penetration, which is why approximately 50% of patients with this disease develop multiple hamartomas affecting the brain, skin, retina, heart, lung, and kidney. 2,6

Tuberous sclerosis was first recognized by Friedrich Daniel von Recklinhausen in 1862, but the term was coined by Bourneville in 1880, and therefore it is also known as Bourneville’s disease. Vougt described the classic triad of epilepsy, mental retardation, and facial angiofibromas, but the triad only presents in 29% of cases and 6% of patients with tuberous sclerosis may not present with any of these findings. 5
The disease may be caused by the mutation of two tumor-suppressing genes that are clinically indistinguishable: TSC1 that is found on chromosome 9 and TSC2 that is found on chromosome 16. The mechanism by which these genes act is only partially understood. It involves the interaction of hamartin and tuberin - two proteins responsible for cell growth and tumor genesis.

The diagnosis of our patient was made from the presence of facial cutaneous lesions and epilepsy, together with bilateral renal angiomyolipoma. The patient refused to have a genetic study carried out.

It is important to point out the characteristics of angiomyolipomas that present spontaneously and those that are associated with tuberous sclerosis, because the symptomaticity of the latter is more selective and potentially symptomatic in relation to pregnancy. The findings reported by Raouf et al. in their series are presented in Table 1.

Tumors that are associated with tuberous sclerosis and are larger than 4 cm are more susceptible to being symptomatic. Pain, hematuria, and retroperitoneal bleeding are the most common manifestations, and if pregnancy is added to size, then diagnosis and therapy become challenging.

The type of medical attention for these patients is still controversial. For asymptomatic tumors, Oesterling et al. propose ultrasound or tomography every six months in tumors larger than 4 cm and every year in those smaller than 4 cm. For symptomatic or bilateral tumors, they suggest selective embolization or conservative renal surgery (partial or tumorectomy).

Radical nephrectomy is carried out when there is uncontrollable bleeding or hemodynamic instability in the cases of large tumors, central localization, or coexisting carcinoma. Other therapeutic options are cryotherapy or thermal tumor ablation through ultrasound or radiofrequency.

In the case of our patient, hematuria persisted significantly, putting the well-being of both the fetus and patient at risk, and therefore the bleeding kidney was embolized.

Yanai suggests that pregestational embolization can reduce the risk of bleeding. However, despite having had a previous abortion, no renal lesions were identified in our patient, and she had not had any prenatal control.

The possibility of nonsurgical management of symptomatic angiomyolipomas has recently been suggested. Rapamycin, also known as sirolimus, is an antibiotic derived from the Streptomyces hygroscopicus bacterium. It is an important immunosuppressant used in organ transplantation and has been shown to be beneficial in 19 years of study.

**CONCLUSIONS**

The association of angiomyolipoma, tuberous sclerosis, and pregnancy is infrequent. Symptomatic renal angiomyolipoma is more common than the spontaneous presentation. When these three factors exist there is a greater risk for complications, and if other aspects such as age and the TSC2 gene carrier genotype are added, prognosis becomes poorer.

Although a matter of debate, management focuses on early diagnosis and minimally invasive methods. Expectant management can be carried out when possible, if the patient remains stable or if embolization is applicable before surgery.

**REFERENCES**


