

BILATERAL RENAL ANGIOMYOLIPOMA IN A PATIENT WITH TUBEROUS SCLEROSIS – CASE REPORT

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BILATERALNI RENALNI ANGIOMIOLIPOM KOD PACIJENTA SA TUBEROZNOU SKLEROZOM-PRIKAZ SLUČAJA

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ABSTRACT

Tuberous sclerosis (Bourneville disease) is a dominant autosomal congenital disease. It is caused by alterations in the ninth or sixteenth chromosome and normally is characterised by a classical triad of mental retardation, epilepsy and sebaceous adenoma. The radiological diagnosis is made by observing some combination of findings: subependymal and periventricular calcifications, cortical tubers, cardiac tumours, renal cysts, and angiomyolipomas. Renal angiomyolipoma (AML) is a benign renal neoplasm, which is composed of fat as well as vascular and smooth muscle elements. AMLs occur in association with tuberous sclerosis in 20% of cases, and they are larger and bilateral, and they affect a younger age group. We report on the case of a 52-year-old woman with abdominal pain, vomiting and anaemia. The initial ultrasound of the abdomen showed bilateral, large, heterogeneous, echogenic masses that occupied the renal fosses, and the kidneys were not observable. The patient was hospitalised for observation and additional radiological diagnostic. The diagnosis of tuberous sclerosis with bilateral renal AML was made based on the presence of typical skin lesions and findings on abdominal and head CT as well as intravenous urography. Currently, despite large bilateral renal AML, her laboratory results showed mild anaemia without renal failure, so the patient has not required surgery.

Key words:
angiomyolipoma, tuberous sclerosis, kidneys

SAŽETAK

Tuberozna skleroza (Bourneville bolest) je autozomalno dominantno nasledno oboljenje. Nastaje kao rezultat alteracija na devetom i šesnaestom hromozomu i najčešće se karakteriše trijadom koja obuhvata mentalnu retardaciju, epilepsiju i prisustvo sebaceoznih adenoma. Dijagnoza se postavlja kombinacijom radioloških nalaza koji uključuju prisustvo paraventricularnih i subependimalnih kalcifikacija, kao i kortikalnih tubera u mozgu, kardioloških tumora, renalnih cista i angimioliipoma. Renalni angimioliipom (AML) je benigni tumor bubrega, koji se sastoji od masti, vaskularnih elemenata i glatkih mišićnih vlakana. Kod bolesnika sa tuberoznom sklerozom renalni AML se javlja u 20% slučajeva i u tom slučaju je obično bilateralni, veći i zahvata mlađu populaciju, nego kad se javlja samostalno. Predstavljamo slučaj pacijentkinje stare 52 godine kod koje se javlja abdominalni bol, mučnina i anemija. Inicijalno, ultrazvuk je pokazao ogromnu, bilateralnu, hiperehogenu masu koja se nalazila u projekciji bubrega, koji nisu mogli biti diferencirani. Pacijentkinja je hospitalizovana u cilju observacije i dodatne radiološke dijagnostike. U skladu sa nalazima kompjuterizovne tomografije abdomena i glave, intravenske urografije, kao i zbog postojanja tipičnih promena na koži, dijagnoza tuberozne skleroze sa renalnim angimioliipomom je postavljena. Međutim, uprkos ogromnim bilateralnim angimioliipomima bubrega, laboratorijski nalazi su ukazivali na blagu anemiju, bez poremećaja bubrežne funkcije, te pacijentkinji nije bila neophodna hirurška intervencija.

Ključne reči:
angimioliipom, bubrezi, tuberozna skleroza



INTRODUCTION

Tuberous sclerosis complex (TSC) is a rare, inherited autosomal dominant multisystem disorder characterised by the potential for the presence of hamartomas (1). Molecular genetic studies have identified two loci for TSC; TSC1 is located on the long arm of chromosome 9 (9q34); TSC2 is located on the short arm of chromosome 16 (16p13.3). Both TSC1 and TSC2 have tumour suppressor activity that, when not activated, leads to uncontrolled cell cycle progression and the proliferation of hamartomas throughout the body (2).

A hamartoma is a benign tumour comprised of an overgrowth of mature cells and tissues that normally occur in the affected tissue, but typically, one element is predominant.

Tuberous sclerosis symptoms include adenoma sebaceum of the skin, angiomyolipomas of the kidney, cortical and subependymal tubers of the brain, rhabdomyomas of the heart and pulmonary lymphangiomyomatosis (LAM). Individual hamartomas are rare in the non-TSC population, so the presence of hamartomas in two different organ systems is considered by some clinicians to be sufficient for the diagnosis (3).

Dermatological Manifestations. The most common dermatological manifestations are hypomelanotic macules or “ash leaf spots” (4). Typically, these lesions are difficult to visualise without the aid of an ultraviolet light (Wood’s lamp). Hypomelanotic macules usually become more apparent with age. Facial angiofibromas (adenoma sebaceum) are composed of vascular and connective tissue elements and typically appear on the face as small pink to red dome-shaped papules in a “butterfly distribution.” The lesions enlarge gradually and increase in number with age. Periungual and unguinal fibromas (Koenen tumours) are smooth, firm, nodular or fleshy lesions that are adjacent to or underneath the nails (5). Toenails are more commonly involved than fingernails (4, 6). Café au lait spots are seen in up to 30% of patients with TSC (7).

A thorough dermatological examination is essential because many TSC’s major features are cutaneous. If hypopigmented macules are not obvious under ambient light, a Wood’s lamp illumination of the skin should be done for every child with infantile spasms, cardiac rhabdomyoma, or renal angiomyolipoma.

Neurological Manifestations. The neurological manifestations are heterogeneous. The spectrum of manifestation ranges from patients with normal intellect and no seizures to those with severe mental retardation and incapacitating seizures. Neurological complications are the most common cause of mortality and morbidity as well as the most likely to affect the quality of life. The most common seizure types are infantile spasms, partial motor seizures, and generalised tonic-clonic seizures (8, 9). Autism, attention deficit, hyperactivity, and sleep problems are the most frequent behavioural disorders (8, 10, 11). The intracranial abnormalities include tubers, subependymal nodules, and subependymal giant

cell astrocytomas (12). No correlation has been found between the number of subependymal lesions and the clinical severity of TSC (13).

Renal Manifestations. Renal complications are the second most common cause of mortality (14). The most common renal lesion is an angiomyolipoma, which occurs in approximately in 80% of cases. Angiomyolipomas are benign tumours comprised of blood vessels with thickened walls, immature smooth muscle cells, and adipose tissue (14, 15). Angiomyolipomas in tuberous sclerosis are larger than the isolated variety, often occur as multiples, are often bilateral, and affect an earlier age group (16, 17). Smaller angiomyolipomas usually do not cause symptoms, but lesions larger than 4 cm in diameter are associated with an increased risk of serious haemorrhage (5, 15). The second most common renal manifestation is a renal cyst, and renal cysts combined angiomyolipomas are characteristic of TSC (5). Renal carcinomas are rare and tend to grow more slowly in patients with TSC than in those found in the general population (15).

Cardiac Manifestations. Cardiac rhabdomyomas usually occur in multiples and are asymptomatic (5, 9). However, these lesions can result in an outflow obstruction, valvular dysfunction, arrhythmias (especially Wolff-Parkinson-White syndrome), and cerebral thromboembolism (13, 18).

Ophthalmic Manifestations. Retinal hamartomas are bilateral and asymptomatic, but some patients have visual impairment as a result of a large macular lesion (13). Angiofibromas may develop on the eyelids (19).

Oral Manifestations. Gingival fibroma occurs in 50% of adults with TSC (19).

Vascular Manifestations. Patients with TSC are at increased risk for arterial aneurysms, which affect the aorta and peripheral arteries (e.g., carotid, renal, intracranial) with potentially appreciable morbid or mortal consequences (18, 19). Histologically, the arterial walls demonstrate a loss of elastin fibres similar to that seen in patients with Marfan Syndrome (18).

Pulmonary Manifestations. The classic pulmonary lesion is lymphangiomyomatosis (LAN), a progressive lung disease seen mainly in adult females (20).

Osseous Manifestations. Osseous lesions on radiographs include bone cysts found mainly in the phalanges of the hands and feet, sclerotic lesions, and periosteal new bone formation (21).

Gastrointestinal Manifestations. Hamartomatous polyps in the rectum are common and are usually asymptomatic (4).

RADIOLOGY FINDINGS

Abnormal radiological findings are important in diagnosing this disease and include lesions found in the CNS, heart, lungs, kidneys, skeleton, and, occasionally, liver, spleen and pancreas.



CT findings

Overall, CT reveals intracranial abnormalities in 85% of patients with tuberous sclerosis. CT readily depicts calcified cortical tubers and calcified subependymal nodules. The frequency of their calcification increases with patient age. Subependymal nodules are found mostly along the lateral ventricles. These nodules may enhance after the intravenous administration of contrast material, but contrast enhancement is more difficult to recognise on CT scans than on other images, particularly in calcified lesions. In 10%-15% of patients, subependymal nodules may transform into giant cell astrocytomas. These tumours are benign and usually occur at or near the foramen of Monro. These lesions typically appear inhomogeneous and usually have an inhomogeneous enhancement pattern after the intravenous administration of contrast material. Frequently, they are calcified, they usually enlarge over time, and they commonly cause obstructive hydrocephalus.

Renal angiomyolipomas often have low attenuation values if they contain sufficient fat, but they are indistinguishable from other renal tumours if they contain little or no lipids. Varying amounts of non-lipid tissue and haemorrhage can be visualised on CT scans of angiomyolipomas. Generally, calcification is not seen in angiomyolipomas. Cystic lesions commonly occur for this disease, and they are well characterised with CT. Multiple cysts can distort the renal collecting system; with this finding alone, tuberous sclerosis is indistinguishable from polycystic kidney disease.

ULTRASOUND findings

On sonograms, the lesions are highly echogenic because of their high fat content. A finding of multiple angiomyolipomas with a high fat content is highly suggestive of tuberous sclerosis. Angiomyolipomas can bleed and cause renal parenchymal haemorrhage as well as subcapsular or retroperitoneal haemorrhage. Cysts almost always occur in multiples; typically, they are bilateral, and on sonograms, cysts are anechoic.

CASE REPORT

A 52-year-old woman at a medical check-up presented with a dull, temporary pain in both flanks that radiated to the bladder, but she had no renal failure. History was significant for one year earlier.

The initial abdominal ultrasound examination showed a large, hyperechogenic mass that occupied the right abdomen and was compressible, which implied intestine. A similar structure was seen in the left abdomen, posteriorly and paravertebrally. The kidneys were not seen either by frontal or by posterior positioning of the sonde. The patient was prescribed additional radiological and laboratory diagnostic and surgical examinations (figure 1).

Abdominal palpation revealed bilateral tender flank masses extending up to both iliac fosses that were insen-



Figure 1. An abdominal ultrasound shows a hyperechogenic mass under the liver in the right abdomen that compresses, which implies intestine.

sible on palpation and lacked peritoneal irritation. They each had a smooth surface of solid consistency, low mobility and clear limits. The patient reported frequent urination without haematuria and temporary pain in both flanks.

Dermatological consultation revealed erythema on the forehead, a paranasal rash with multiple sebaceous adenomas around the nose and nasolabial folds (figure 2), some hypomelanotic macules, and fibromatous tumours (Koen) under the toenails with disfiguration of the nails.

Laboratory analysis revealed mild anaemia (RBC 2, 12; Fe 6, 5; Hgb 96) with normal levels of creatinine and urea (Cre 89; Urea 5, 8) that suggested the renal profile was normal.

IMAGING FINDINGS:

Abdominal contrast-enhanced CT revealed a large tumour in the retroperitoneum with primarily fat-equivalent attenuation (image density was -50 HU) that completely replaced both of the kidneys. Intraperitoneal structures



Figure 2. Erythema on the forehead, paranasal rash, and multiple facial angiofibromas around the nose and nasolabial folds are dermatological manifestations.

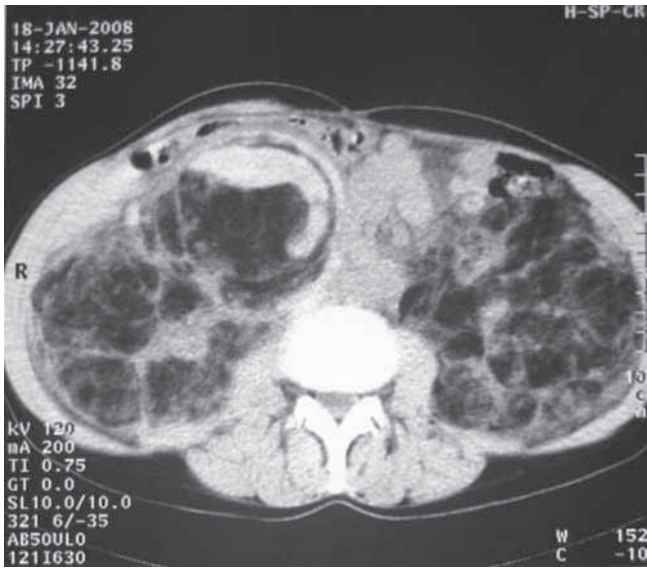


Figure 3. As seen on the abdominal CT, there is a large tumour in the retroperitoneum with predominantly fat-equivalent attenuation that replaced both the kidneys entirely and displaced intraperitoneal structures anteriorly.

were displaced anteriorly, and the mass extended as far as the pelvic region (figure 3).

The head CT revealed cortical and subcortical redudctive alteration: multiple calcified subependymal and paraventricular tubers, subcortical calcified nodules in the left hemisphere of the cerebellum and benign white matter lesions (figure 4).

The chest CT revealed bilateral, symmetrical, and diffuse distribution of small air cysts with thin regular walls and normal lung parenchyma between the cysts.

Intravenous urography showed a compressed and extended pyelic system of both kidneys. Kidney structure was not discernable. The contrast was excreted, and the ureters were visualised bilaterally. The bladder was normal (figure 5).

Echocardiography and chest x-ray revealed no abnormalities.

Based on these examinations, the diagnosis was Bournville-Pringle syndrome, tuberous sclerosis. Despite the bilateral large retroperitoneal angiomyolipoma of the kidneys, the patient's condition was satisfactory, and the renal profile was normal. For that reason, there will further observation without surgery.

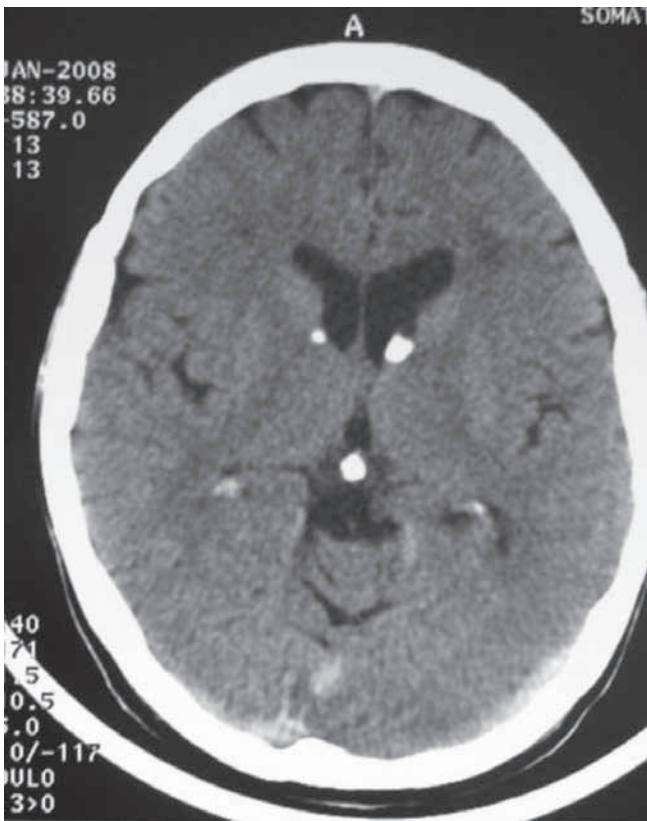


Figure 3. As seen on the abdominal CT, there is a large tumour in the retroperitoneum with predominantly fat-equivalent attenuation that replaced both the kidneys entirely and displaced intraperitoneal structures anteriorly.



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DISCUSSION

Angiomyolipomas are uncommon, benign, renal neoplasms comprised of blood vessels with thickened walls, immature smooth muscle cells and mature adipose tissue. They occur as isolated, sporadic entities in 80% of cases. The remaining 20% develop in association with tuberous sclerosis (16, 17). This tumour is one of the major diagnostic criteria of tuberous sclerosis (16). The occurrence of angiomyolipomas in the tuberous sclerosis complex can be up to 80%. Although the histological appearance of angiomyolipomas in these two entities is identical, renal angiomyolipomas with tuberous sclerosis are distinctly different from those without tuberous sclerosis. Angiomyolipomas in association with tuberous sclerosis manifest at a younger age. They are likely to be larger and bilateral and are prone to grow and need surgical treatment (17). In the series by Steiner et al., the average size of AML in patients with TS is 9.6 ± 4.8 cm and 4.1 ± 3.4 cm in those without TS (17) (Table 1).

Angiomyolipoma – benign mesenchymal tumour	
ISOLATED (80%)	ASSOCIATED WITH TS (20%)
<ul style="list-style-type: none"> - usually solitary - unilateral (80% on the right side) - not associated with TS - mean age of incidence: 40-49 years - much more common in females 	<ul style="list-style-type: none"> - occurs in 80% of patients with TS - commonly large - usually bilateral - usually multiple - may be only evidence of TS - mean age of incidence: 12-19 years - equal incidence in males and females

Table 1. Types of angiomyolipomas. Differences between the isolated form and the form associated with TS.

The hormonal influences of the steroid receptors in the muscle cells may explain the differences in tumour behaviour seen during different periods of life, with greater tumour growth in postpubertal period and during pregnancy (22). L'Hostis et al. observed the presence of both progesterone and oestrogen receptors in angiomyolipomas, and they found that progesterone and oestrogen immunoreactive angiomyolipomas were predominantly found in women and in patients with tuberous sclerosis (23). These findings may further explain the more aggressive nature of the disease process in patients with tuberous sclerosis, the hormonal potentiation of tumour growth and haemorrhage in conditions such as pregnancy, and the overwhelming female predominance in the sporadic form of angiomyolipoma without tuberous sclerosis (23, 24-26).

Angiomyolipomas remain silent and are commonly incidental findings, but they may manifest with symptoms of abdominal and flank pain, gross haematuria, nausea, vom-

iting, fever, abdominal distension or simply as a mass (16, 17, 27, 28). Common findings include a palpable mass, abdominal tenderness, haematuria, anaemia, shock, hypertension, urinary tract infections, and renal failure. These signs and symptoms are usually a result of the effects of the mass and haemorrhage (16). The propensity to haemorrhage is related to multiple factors: focal deficiencies of elastic tissue in abnormally rigid and thick blood vessels, hypervascularity, and venous invasion (29-31). The defects in the vessel's elastic tissue also predispose these lesions to develop aneurysms. Our patient presented late with abdominal pain and mild anaemia but no renal failure.

With advances in cross-sectional imaging, the diagnosis of renal angiomyolipoma can usually be made confidently without surgery. The demonstration of fat on renal ultrasound and CT can accurately diagnose angiomyolipoma in 95% of cases (16). Angiomyolipomas are well-defined hyperechoic masses based on ultrasonography (US) regardless of the relative fat component (32). Angiomyolipoma fat is easily identified on CT, which helps to make the radiological diagnosis. Demonstration of intratumoural fat attenuation is almost pathognomonic for this lesion (16, 17, 27, 28). Single or multiple well-circumscribed renal cortical tumours containing tissue with fat attenuation of less than -20 HU are characteristic findings of angiomyolipoma on non-enhanced CT (16). In the present case, a diagnosis of AML was made based on typical ultrasound and CT findings.

Angiomyolipomas are at risk for spontaneous haemorrhage. Lesions greater than 4 cm are at greater risk of serious spontaneous haemorrhage and need to be evaluated. Tumour diameter >4 cm has also been used as a criterion for prophylactic treatment because many studies show a higher frequency of haemorrhagic complications with larger tumours (17, 33). However, according to Antonopoulos et al. (34), these tumours do not have to be large (>4-cm diameter) before serious life-threatening haemorrhage can occur, as previous studies have suggested, and at least one study has shown that smaller tumours <4 cm have a more rapid doubling time (35). Especially, when the lesions are >10 cm, the preferred route of treatment is partial nephrectomy or selective arterial embolisation (16, 17). Massive retroperitoneal haemorrhage due to AML, also known as Wunderlich's Syndrome, has been found in up to 10% of patients (36). Although many angiomyolipomas do not show growth over time, those that occur with TSC are more likely to show progressive evolution. Conservative observation and follow-up examinations of asymptomatic patients with tuberous sclerosis and angiomyolipoma are recommended with bi-annual or annual imaging: US, CT, or MR imaging.

Selective arterial embolisation has been effective in the treatment of acute haemorrhage, with or without later surgery, or as initial treatment of angiomyolipoma (37-39). Although arterial embolisation is minimally invasive, it does not preserve renal function. It only has a temporary effect, it requires close clinical observation because of associated



complications, and, as a rule, it is ineffective when used alone. Regarding surgical treatment, a tumourectomy, partial nephrectomy, or total nephrectomy may be done. The surgical treatment that preserves the largest amount of renal tissue is tumour enucleation, which has been performed with excellent results, even for large angiomyolipomas (>20 cm). Tumour enucleation is practically applicable for patients with tuberous sclerosis who present with multiple and bilateral lesions (39-41). Total nephrectomy should be used very rarely; it is only justified in cases of uncontrollable bleeding, when there is risk to the patient's life, in central tumours, in the presence of extensive necrosis, when there is inflammation of the renal tissue, or when there is a diagnosis of renal carcinoma in the same kidney. Recently, cryotherapy has been suggested as a therapeutic option and may be associated with laparoscopy (42). The primary treatment objective of angiomyolipoma is the preservation of renal function, principally in those cases in which it is associated with tuberous sclerosis and the lesions are generally larger, multiple, bilateral, and recurring. Amongst the therapeutic options, tumour enucleation increases the potential for preservation of the renal tissue, followed by selective arterial embolisation and cryotherapy. Embolisation primarily controls the bleeding in the acute phase but may lead to greater loss of the renal function.

In conclusion, the basis of management for angiomyolipoma is to preserve of renal tissue and function, which can be effectively achieved with nephron-sparing surgical procedures such as tumour enucleation. However in some circumstances, it is necessary to do selective angioembolisation, partial nephrectomy, or even total nephrectomy. Especially in patients with tuberous sclerosis with large bilateral and multiple tumours, the aim of treatment is to preserve the greatest amount of efficient renal function.

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