

Concurrent Hepatic and Ruptured Renal Angiomyolipoma in Tuberous Sclerosis Complex

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Angiomyolipoma of the liver or kidney is one of the clinical manifestations of tuberous sclerosis complex. However, concurrence of angiomyolipoma in both liver and kidney associated with tuberous sclerosis complex is a rare entity. Renal angiomyolipomas with large aneurysms confer a higher probability of rupture as compared to small aneurysms. Herein, we document a case of tuberous sclerosis coexisting with hepatic and renal angiomyolipoma in a 37 year-old woman who presented with an acute abdomen due to ruptured tumor. Computed tomography of the abdomen revealed multiple tumors over the bilateral kidneys and liver. A right nephrectomy was performed. During surgery, a liver biopsy was performed from which a preliminary diagnosis of necrosis was established. However, immunoreactivity staining using monoclonal antibody HMB-45 (Human Melanoma, Black) led to the final diagnosis of angiomyolipoma. We emphasized that pathologists and clinicians should be aware that cases of tuberous sclerosis complex may be associated with renal and hepatic angiomyolipoma. To avoid an inappropriate diagnosis, before diagnosing liver necrosis, immunohistochemical staining for HMB-45 is recommended. (*Chang Gung Med J* 2004;27: 696-700)

Key words: angiomyolipoma, tuberous sclerosis, liver, kidney.

Tuberous sclerosis complex (TSC) involves multiple organs, including the brain (cortical and sub-cortical tubers, subependymal nodules, and giant cell astrocytomas), the kidney (angiomyolipomas, cystic carcinomas), the skin (hypomelanotic macules, shagreen patches, facial angiomyolipomas, periungual fibromas), the eye (retinal hamartomas) and the heart (rhabdomyomas). Ishak first described hepatic angiomyolipoma (AML) in 1976. Since then more than 100 cases have been reported in the English literature.^(1,2) However, fewer than 10% of hepatic AML have been associated with tuberous sclerosis.^(2,3) Most tuberous sclerosis is associated with either renal AML or with multiple liver AML alone.⁽²⁻⁴⁾ Coexistence of renal AML and hepatic

AML is a rare condition. This article reports a woman with hepatic AML, who also had extensive bilateral renal AML and the facial characteristics of TSC.

CASE REPORT

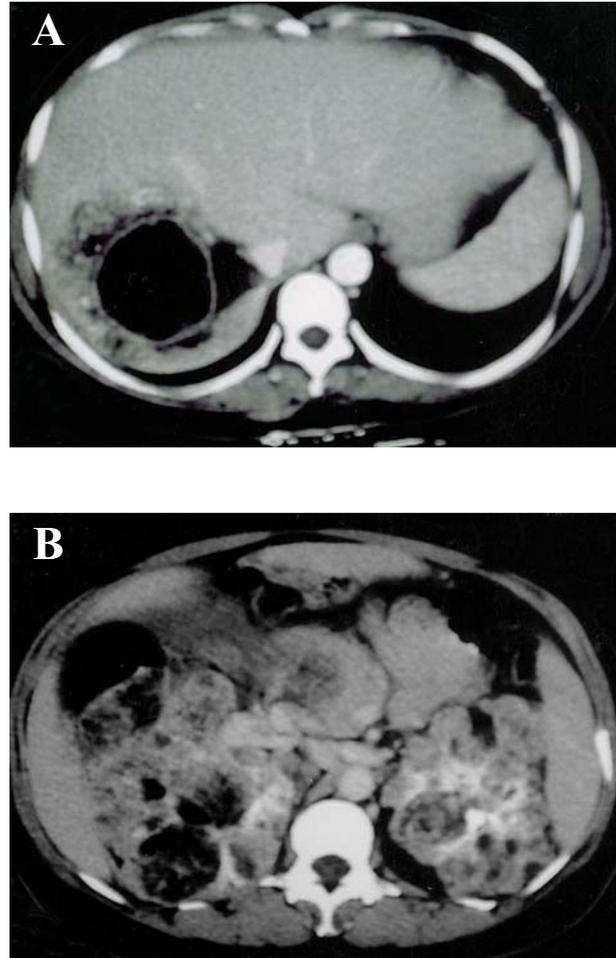
A 37-year-old woman was hospitalized in our department for 2 weeks because of abdominal pain and fullness. On admission, physical examination revealed an angiomatous lesion, compatible with angiofibroma over her face. In addition, a mass lesion was visible over the right upper quadrant of her abdomen. Her history was unremarkable. No family members had suffered tuberous sclerosis. Her

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complete blood cell count was red blood cell count 2.52 million/mL, hemoglobin 7.3 gram%, hematocrit, 21.9%, platelet 177,000/ mL and white blood cell count 12.6×10^9 /liter (with the segment 93%, and lymphocyte 7%). Biochemical data showed serum creatinine 1.3 mg/dl, blood urea nitrogen 15 mg/dl, albumin 28 g/L, total protein 60 g/L, calcium 7.0 mg/dl, sodium 138.2 meq/L, potassium 4.37 meq/L, aspartate aminotransferase 75 U/L, alanine aminotransferase 10 U/L, total bilirubin 0.7 mg/dl and C-reactive protein 17.5 mg/L. The serum alpha-fetoprotein (AFP) level was <3 ng/ml (normal <20 ng/ml). The carcinoembryonic antigen (CEA) level was <0.5 ng/ml (normal range <5 ng/ml). The carbohydrate antigen 199 (CA-199) level was 9.21 U/ml (normal range <37 U/ml). The cancer antigen-125 (CA-125) level was 85.9 U/ml (normal range <35 U/ml). Urinalysis showed a specific gravity of 1.005, pH 6.5, no protein, no red blood cells, and no white blood cells. Ultrasonographic examination of the liver indicated a hyperechoic lesion of 10×10 cm over segments 6 and 8 of the right liver lobe. Computed tomography (CT) of the abdomen revealed tumors over the bilateral kidneys and liver (Figs. 1A-B). CT of the brain revealed no abnormality.

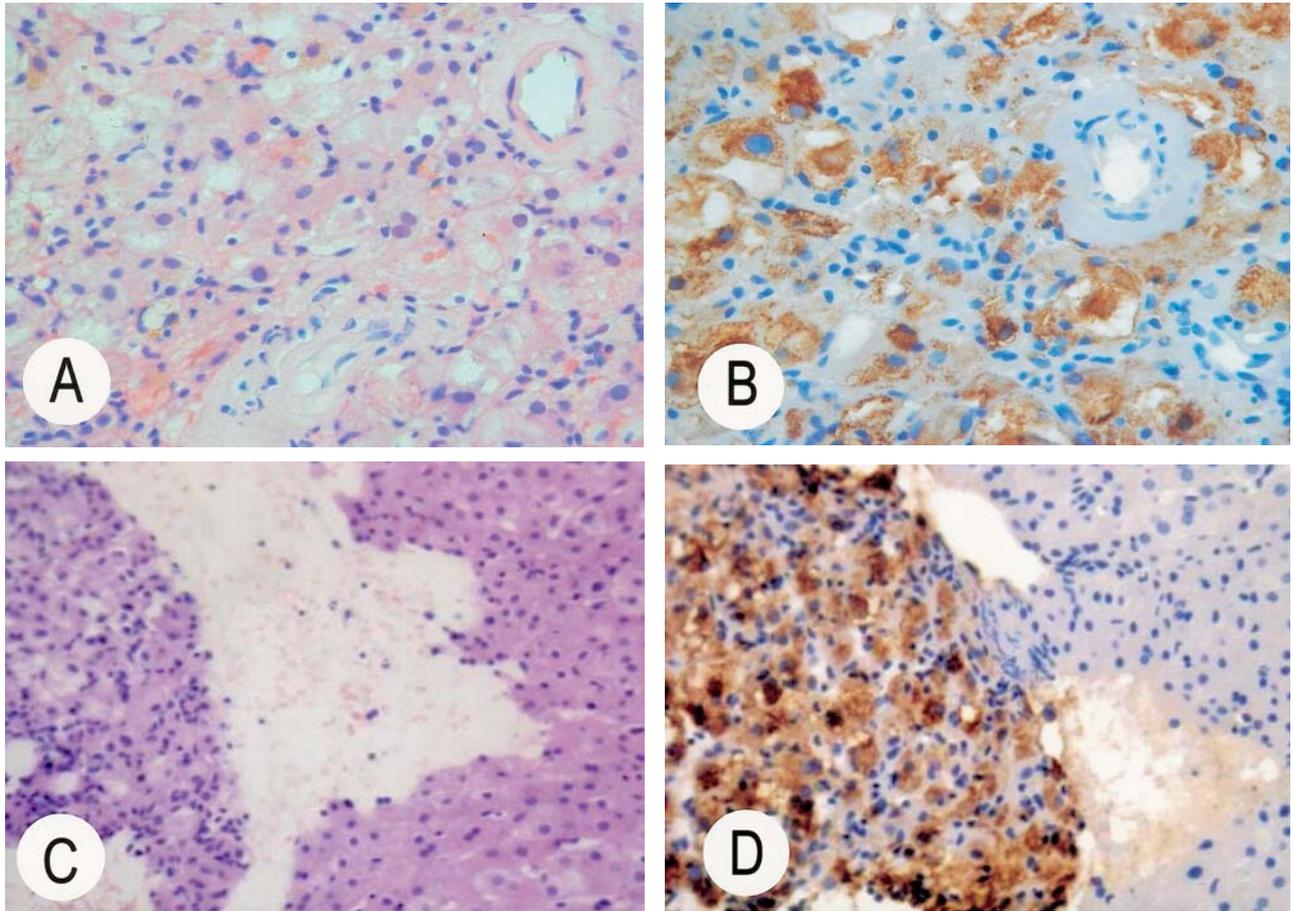
During hospitalization, the acute abdomen persisted and signs of peritonitis developed. Emergency laparotomy with a right nephrectomy was then performed. Meanwhile, a liver biopsy was also done. A gross pathologic examination of the right kidney revealed a soft tumor, measuring $20 \times 18 \times 6$ cm, involving the entire external surface of the right kidney. The tumor was well-circumscribed with smooth surface and globular appearance. The cut surfaces were yellowish and soft with extensive focal hemorrhage and necrosis. The pelvis and the calyces were partially affected. Microscopically, the tumor exhibited a mixture of mature adipose tissue, tortuous thick-walled vessels and smooth muscle (Fig. 2A). The smooth muscle cells appeared either spindle-shaped or epithelioid. The focal areas exhibited extensive hemorrhage and necrosis admixed with dense acute inflammatory cell infiltrates, indicating a perforative lesion. Further immunohistochemical study gave a negative result for desmin but strong immunoreactivity for HMB-45 (Human Melanoma, Black) (Fig. 2B), leading to a diagnosis of angiomyolipoma. The liver biopsy also revealed a necrotic-



Figs. 1 (A) Enhanced CT scan of abdomen revealed a lobulated mass in the right lobe of the liver, containing fat and soft tissue components. (B) Enhanced CT scan of abdomen revealed bilateral enlarged and deformed kidneys, which contained a large non-homogeneous tumor mass with fatty components.

like lesion in some tissue fragments. The preliminary diagnosis following the liver biopsy was necrosis and degeneration (Fig. 2C). However, further immunohistochemical staining for HMB-45 was strongly positive in the degenerated and necrotic cells (Fig. 2D). The diagnosis of hepatic AML was thus verified.

A follow-up abdominal CT, 12 months after surgery revealed remaining angiomyolipomatous lesions in the left kidney and liver. No further surgi-



Figs. 2 (A) The micro photograph of the renal tumor tissue shows an admixture of mature adipose tissue, thick-walled vessels and smooth muscle (H&E stain, 100 \times); (B) HMB-45 immunoreactivity is detected in some tumor cells (paraffin immunohistochemical stain, 100 \times); (C) The left part of the photograph depicts fragmented tissue as degenerate features admixed with chronic inflammatory cell infiltrate. The right part of the photograph shows normal liver parenchyma (H & E stain, 100 \times); (D) The immunohistochemical staining of HMB-45 shows strongly positive stainable in tumor cells within the fragmented degenerative-like tissue (left portion) while the liver parenchyma remains not stainable (right portion) (paraffin immunohistochemical stain, 100 \times)

cal intervention was performed and the patient remained well.

DISCUSSION

Forty to fifty percent of patients with renal AML have been estimated to have underlying TSC, and approximately 60% to 80% of patients with TSC have renal angiomyolipoma.⁽⁵⁻⁷⁾ On the contrary, hepatic AML associated with TSC are rare, accounting for 6% to 25% of cases.^(3,8) In 1970, Ramchand et al. described liver lipoma in a patient with TSC.⁽⁹⁾

Since then, over 80 cases have been reported in the English literature. In 1994, Aktaka Nonomura et al. reviewed 52 cases of hepatic AML.⁽⁴⁾ Only 3 (approximately 5.8%) patients had both TSC and renal AML. In the series of Tsui et al. which included a total of 30 cases of hepatic AML, only 3 patients (10%) presented evidence of TSC. All 3 also had renal AML.⁽²⁾ Yeh et al. reported that 2 of 8 cases of hepatic AML had concurrent renal AML.⁽³⁾ One of the 2 patients had tuberous sclerosis.

Most hepatic AML are solitary, and most of these are not associated with TSC. In fact, the associ-

ation of hepatic AML with TSC increases when multifocal tumors are present or hepatic AML coexists with renal AML.^(2-5,8,10) Our patient had a solitary hepatic AML and bilateral renal AML. However, the clinical presentation of rupture of right renal AML may mimic the presentation of liver or renal abscess. CT of the abdomen and the pathological findings assisted by immunostaining for HMB-45 are effective tools in making a differential diagnosis.

TSC is a genetic disease that affects multiple organs. Mutations of two different genes (TSC1 at 9q34 and TSC2 at 16p13.3) have been demonstrated to be associated with TSC.⁽¹¹⁾ It is inherited as an autosomal dominant trait, although a high rate of spontaneous mutation in one of the TSC genes has been determined (65-75% of cases arise from new mutations).⁽¹¹⁾ No family member of our patient had tuberous sclerosis. Although the clinical expression of TSC is highly variable, its expression is not determined by specific gene mutation, because even affected members of the same family frequently develop very different manifestations. The phenotype cannot be precisely predicted by which of the two genes is affected. In fact, individuals with the TSC1 mutation or mutated TSC1 seem to have a lower less risk of intellectual impairment whereas those with TSC2 mutations probably have a higher risk of renal cysts.⁽¹¹⁾

Although both renal and hepatic AMLs may be diagnosed as probable TSC, according to the Tuberous Sclerosis Alliance, some cases of renal and hepatic AML without evidence of TSC have been reported.^(5,10)

The hallmarks of AML of renal or hepatic tissue include the presence of an admixture of adipose tissue, smooth muscle and vasculature components, in various proportions. Occasionally, in liver biopsy specimens, unusual histological features, such as a leiomyomatous element mimicking liver tissue, as in the presented case, make the diagnosis difficult.⁽⁴⁾ Under these conditions, immunohistochemical evaluation by staining with HMB-45, a melanoma-related antigen which is usually positive for renal and hepatic AML, is particularly helpful.^(12,13) In fact, the diffi-

cult task in diagnosing hepatic AML is to remember that AML can arise in the liver, especially when TSC is associated with renal AML. Pathologists and clinicians should always be aware of the occurrence of coexistent renal and hepatic AML to prevent a misdiagnosis.

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結節性硬化症同時併發肝臟及破裂之腎臟血管肌脂肪瘤

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肝臟或腎臟的血管肌脂肪瘤是結節性硬化症的臨床表現之一。然而，結節性硬化症同時發生肝臟及腎臟的血管肌脂肪瘤是一個罕見的疾病。越大的腎臟的血管肌脂肪瘤其破裂的機率也越大。在此我們報告同時發生肝臟及腎臟的血管肌脂肪瘤一個結節性硬化症病例，一開始是以腫瘤破裂的急性腹痛為表現。腹部電腦斷層顯示肝臟與雙側腎臟有多發性的腫瘤。因為腫瘤破裂，右側腎臟被切除。同時肝臟切片初始診斷為壞死組織。然而使用HMB-45染色的免疫活性測定診斷為血管肌脂肪瘤。我們所強調病理學家與臨床醫師應考慮到結節性硬化症可能併發肝臟或腎臟血管肌脂肪瘤。為了避免不適當的診斷，建議使用HMB-45的免疫組織化學染色。(長庚醫誌 2004;27:696-700)

關鍵字：肝臟和腎臟血管肌脂肪瘤，結節性硬化症。

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