Skin and Visceral Manifestations in Tuberous Sclerosis

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Tuberous sclerosis complex (TSC) is a multisystem autosomal dominant disorder due to mutations of either the *TSC1* gene on chromosome 9 or the *TSC2* gene on chromosome 16, with an incidence of approximately 1 in 5000–10,000 live births. TSC often causes neurologic disorders, including epilepsy, mental retardation and autism. Additional major features are skin, kidney, lung, heart, liver and eye manifestations [1]. TSC may occur as a familial hereditary or sporadic mutation. *TSC2* mutations are four times more common than those of *TSC1* in sporadic cases, while the prevalence of *TSC1* and *TSC2* mutations among the familial cases is similar; *TSC1* mutations appear to be slightly higher. As a result of the high variability of mutations (somatic mosaicism of different degree and the differences between *TSC1* and *TSC2* genes), there is a wide clinical spectrum and severity of TSC. The two-hit hypothesis of Knudson, the loss of heterozygosity for both alleles of either *TSC1* or *TSC2*, appears to be necessary for the development of lesions [2]. Among patients meeting the clinical criteria for a diagnosis of TSC, 10 to 25% have no identifiable mutations. These patients generally have milder clinical disease, with a lower incidence of mental retardation and seizures [3].

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A 40 year old man, already diagnosed with TSC, presented to our department due to fever, pleural pain and clear productive cough accompanied by pain in the right chest and back. He presented with characteristic skin features: malar angiofibromas [Figure 1], shagreen patches on the lower back [Figure 2], and ash-leaf spots all over the body (these frequently require Wood's lamp, i.e., ultraviolet light to be recognized).

Visceral involvement was also demonstrated by the computed tomography scan exhibiting renal angiomyolipomas (AML) [Figure 3], which are the most frequent renal manifestations of TSC, presenting in about 55–75% TSC patients [3]. Because these tumors have abnormal vasculature and often contain aneurysms [Figure 4], spontaneous bleeding is a life-threatening complication. Large AMLs can be treated with selective renal artery embolization. An interesting study by Yamakado et al. [4] investigated the association between AML size, aneurysm size and rupture. Those authors suggested that the size of associated aneurysms may be more significant in predicting the possibility of rupture. In their study all ruptured aneurysms were more than 5 mm, 88% > 9 mm; the smaller aneurysms (< 5 mm) were significantly less likely to require intervention. In addition, several recent case reports and clinical trial studies in TSC patients with renal AMLs confirmed that AMLs regress in response to rapamycin therapy, thereby decreasing

Figure 1. Malar angiofibromas

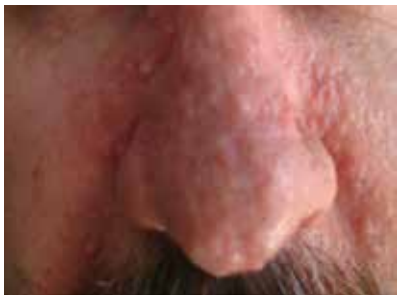


Figure 2. Shagreen patches on the lower back

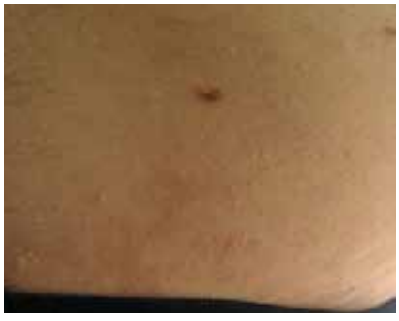


Figure 3. Visceral involvement. **[A]** AML in the upper pole in the right kidney, and **[B]** bleeding in the lower pole in the left kidney

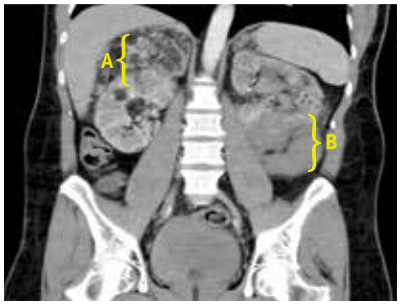
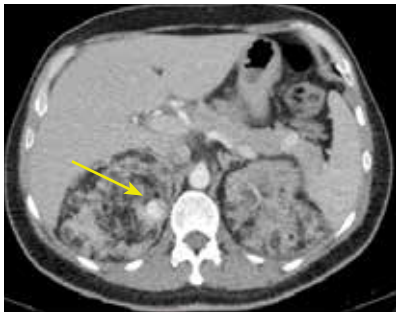


Figure 4. Aneurysm in right kidney



the risk for bleeding. Rapamycin is an inhibitor of mTOR (protein kinase that controls cell growth) which is continually active in TS patients. However, after discontinuation of rapamycin, variable regrowth of AMLs was observed [5].

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