

Coexistence of tuberous sclerosis complex and malignant melanoma

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ABSTRACT Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterised by widespread hamartomas in organs such as the skin, brain, heart, lung, liver and kidney. Although associations of TSC with hamartomas, angiomyolipomas and fibromas have been reported, there has been no report of its association with malignant melanoma. Herein, we describe a 31-year-old man with malignant melanoma associated with TSC. The patient had a history of epilepsy, multiple hypomelanotic macules, periungual fibromas and multiple hepatic lesions. Malignant melanoma was diagnosed by hepatic biopsy. To the best of our knowledge, this is the first report of malignant melanoma coexisting with TSC in the literature. We also present and discuss the imaging findings, prognosis, underlying mechanisms and practical approaches in relation to the disease.

Keywords: angiofibroma, malignant melanoma, neurofibroma, tuberous sclerosis, tumorigenesis

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterised by seizures, mental retardation, skin lesions and hamartomatous lesions in several organs. These lesions include renal angiomyolipomas and cysts, facial angiofibromas, cardiac rhabdomyomas, subependymal giant cell astrocytomas and cortical tubers.⁽¹⁾ The prevalence of TSC is estimated to range from 1/6,000 to 1/9,000 due to undiagnosed or asymptomatic patients.⁽²⁾ Multiple hamartomas or tumours may develop in multiple organs. The genes affected in TSC are *TSC1* (located on 9q34) and *TSC2* (located on 16p13.3), which are normally expressed in neuroendocrine cells and are both tumour growth suppressors.^(3,4) *TSC1* and *TSC2* encode the proteins hamartin and tuberlin, respectively, which form the TSC1-TSC2 complex and share a common signalling pathway. Inactivation of these genes causes the development of a wide range of hamartomatous lesions.⁽⁴⁾ Lesions formed in the brain can lead to symptoms such as seizures, intellectual disability and skin angiofibromas.⁽⁵⁾

In this report, we present the case of a 31-year-old patient with coexistent malignant melanoma (MM), cerebral-renal angiomyolipomas and skin lesions in association with TSC. To the best of our knowledge, the association of MM with TSC has not been previously reported in the literature.

CASE REPORT

A 31-year-old man presented to the Urology Clinic at the Faculty of Medicine, University of Cukurova, Saricam-Adana, Turkey, with erectile dysfunction. Ultrasonography of the scrotum and abdomen revealed varicocele and multiple masses, and the patient was referred to the Department of Medical Oncology at our hospital for further management. On physical



Fig. 1 Photograph shows multiple adenoma sebaceum on the patient's face.

examination, we found multiple adenoma sebaceum on the patient's face (Fig. 1). Subungual fibromas, hepatomegaly, and multiple hypomelanotic, depigmented macules on the patient's back, body, face and nape, were also found. The patient had a 25-year history of epilepsy.

Laboratory investigations only detected normocytic anaemia. Subsequent magnetic resonance imaging of the brain revealed subependymal calcifications in the bilateral cerebral parenchyma and subcortical tubers in the white matter of the frontal lobe (Fig. 2). The patient was referred to the Dermatology Department, where the skin lesions were interpreted as neurofibroma. However, the patient had no family history of TSC.

Positron emission tomography/computed tomography (PET/CT) of the abdomen revealed a hypervascular mass

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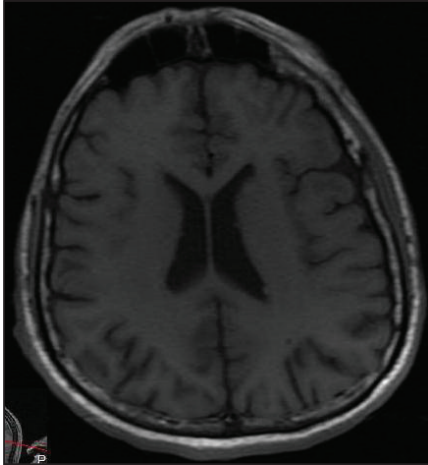


Fig. 2 MR image of the brain shows subependymal calcifications in the bilateral cerebral parenchyma and subcortical tubers in the white matter of the frontal lobe.

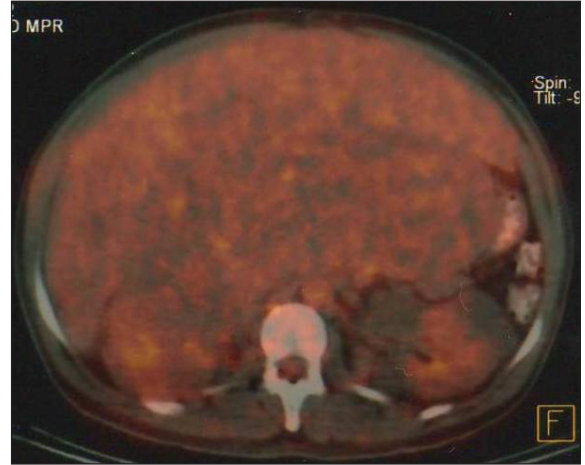


Fig. 3 PET/CT image of the abdomen shows multiple cysts in both kidneys and similar masses in the adrenal gland and spleen on the left side.

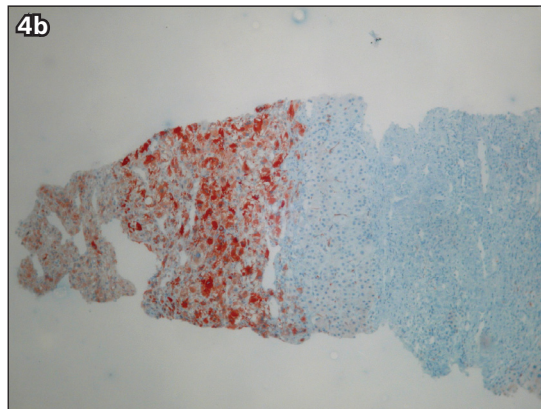
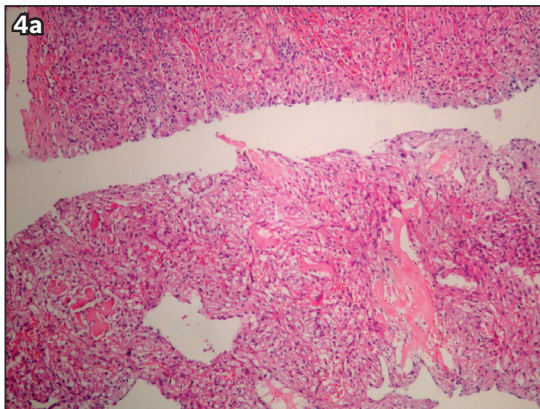


Fig. 4 Photomicrographs show (a) oval-round tumour cells with hyperchromatic nucleus fusiform and polygonal cytoplasm arranged in solid pattern (Haematoxylin & eosin, × 100); and (b) positive immunohistochemical staining of the tumour cells with Melan A (Melan A, × 100).

with an axial size of 25 cm in the liver. Multiple cysts in both kidneys and similar masses in the adrenal gland and spleen on the left side were also observed (Fig. 3). A tru-cut liver biopsy was performed and findings of the histopathological examination were compatible with MM. Immunohistochemically, human melanoma black-45 (HMB-45), Melan A, S100 and vimentin were found to be positive, but HepPar-1, CD 10 and keratin were negative (Fig. 4).

Temozolomide (200 mg/m²) was applied and disease progression was observed following a four-cycle treatment, using CT of the abdomen. In spite of the four cycles of ipilimumab (3 mg/kg) administered to the patient, the response was only stable disease.

DISCUSSION

TSC is a genetic disease usually caused by sporadic genetic mutations. Inheritance of the disease, with an autosomal dominant pattern, has also been reported.^(1,4) The genes affected in TSC are *TSC1* and *TSC2*,⁽³⁾ and mutations in these genes are related to various risks of malignancy. For instance, an increased incidence of *TSC2* mutations has been reported in patients with renal cell carcinoma.⁽⁴⁾

The TSC genes play a significant role in the phosphoinositide 3-kinase (PI3K) pathway and are a mammalian target of rapamycin (mTOR), a molecule that plays a key role in the pathogenesis of TSC. TSC genes also play a significant role in survival and protein production.^(4,6) *TSC2* is also involved in the regulation of apoptosis. Dysregulation of the apoptotic pathway, usually implicated in a wide range of malignancies, raises the likelihood that the activation or suppression of *TSC1* and *TSC2* could contribute to the occurrence of some sporadic cancers such as renal cell carcinomas and sporadic astrocytomas.⁽⁴⁾

PI3K is mainly hyperactivated by the loss of phosphatase and tensin homologue (PTEN), and results in the phosphorylation and activation of the survival gene *AKT* and the subsequent stimulation of the mitogenic mTOR pathway.⁽⁷⁾ Although the association between TSC and MM is not clear, there is a common pathway in the development of both these diseases.

Benign lesions (e.g. hamartomas, angiomyolipomas, angiofibromas and rhabdomyomas) occur frequently in TSC, with the most characteristic neoplasms occurring in the brain, kidney, liver, lung and heart.^(1,3) However, in recent

Table 1. Reports of patients with non-cerebral and non-renal malignancies in patients with tuberous sclerosis complex in the literature.

| Study (yr) | Age (yrs) | Gender | Family history | Type of malignancy | Stage |
|---|-----------|--------|----------------|----------------------------|---------|
| Bonetti et al (2001) ⁽⁶⁾ | 28 | Female | Unknown | Abdominopelvic sarcoma | IV |
| Williams et al (2008) ⁽⁹⁾ | 41 | Female | No | Breast | IV |
| Yang et al (2008) ⁽¹⁰⁾ | 51 | Female | Unknown | Hepatocellular carcinoma | II |
| Ahmed et al (2009) ⁽⁴⁾ | 45 | Female | Unknown | Gastric | IV |
| Sreenarasimhaiah et al (2009) ⁽¹¹⁾ | 24 | Male | Unknown | Somatostatinoma, leukaemia | IV |
| Rai et al (2011) ⁽¹²⁾ | 16 | Female | No | Neurocutaneous melanoma | Unknown |
| Tandstad et al (2012) ⁽¹³⁾ | 25 | Male | Unknown | Testicular | IV |
| | 34 | Male | Yes | Testicular | IIB |
| | 35 | Male | Yes | Testicular | IB |
| Present study (2013) | 31 | Male | No | Malignant melanoma | IV |

literature, TSC has been associated with testicular, gastric, somatostatinoma, hepatocellular, breast, giant congenital melanocytic nevus and sarcoma types of cancer (Table 1).^(4,8-13)

The transformation of a subependymal nodule into a subependymal giant cell tumour is usually a gradual process, and renal cell carcinomas may develop within dysplastic epithelial cysts in 2%–3% of these patients.⁽⁵⁾ Our patient, in whom skin lesions were observed since childhood, was thought to have MM transformation of TSC at diagnosis (i.e. at the age of 31 years). Although TSC is not considered to be a risk factor for MM, we speculated tumour development in our patient for the following reasons: (a) the activation of neurofibromatosis type 1 gene (*NF1*), which has a significant role to play in the development of cutaneous neurofibromas in neurofibromatosis type 1 disease, is regulated by *TSC2*,⁽¹⁴⁾ and (b) *TSC2* regulation has a significant role in the formation of skin lesions, and mutated *TSC2* may increase the risk of malignancy.^(10,15)

In conclusion, we herein report the hitherto unknown association between TSC and MM. Melanoma is a heterogeneous and aetiologically complex disease. The interaction of genetic, host and environmental factors are efficacious in the development of both familial and sporadic cases of MM. As ultraviolet radiation is a particularly important environmental risk factor,⁽¹⁵⁾ patients with TSC should refrain from solar exposure. Although TSC is frequently associated with benign lesions, malignant transformation was observed in our patient. Given the close interrelationship among genetic defects, and the common pathways in the development of TSC and the tumorigenesis of MM, clinicians should have an awareness of the possibility of malignant transformation of skin lesions in patients with TSC. Patients with TSC should be closely observed due to the potential risk of malignant transformation of skin lesions. More comprehensive research is needed to define the pathways affected in cases where TSC is associated with tumour development.

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