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Case Report

Massive hepatic angiomyolipoma in a young woman with tuberous sclerosis complex: Significant clinical improvement during tamoxifen treatment☆

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***Background/Aims*: Isolated liver angiomyolipomas (AMLs) occur in about 40% of TSC patients. Because of their slow growth, these tumors are often asymptomatic. Since AMLs express estrogen and progesteron receptors we suggest the possible benefits of tamoxifen for the treatment of liver AMLs.**

***Methods*: We report the case of a 26-year-old female affected by tuberous sclerosis (TSC2) with cerebral, renal and hepatic involvement admitted to the Liver Unit for severe malnutrition, anorexia and abdominal pain. MRI showed a grossly enlarged liver, causing severe gastric compression. The liver was entirely filled with multiple nodular lesions of different sizes. Liver biopsy showed tumoral tissue with microscopic and ultrastructural features of angiomyolipoma. All liver function tests were repeatedly normal. Prior to considering the patient for partial hepatectomy, she was administered tamoxifen (20 mg b.i.d).**

***Results*: After 6 months of tamoxifen treatment a greatly improved quality of life and a significant weight gain were observed. After 12 months the clinical conditions further improved and the MRI showed a significant reduction of the largest lesion with a liquid central area and a diminished compression of the stomach.**

***Conclusions*: This is to our knowledge the first report in which tamoxifen has been successfully used in a TSC patient with multiple liver angiomyolipomas.**

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***Keywords*: Tuberous sclerosis complex; Tamoxifen; Angiomyolipoma**

1. Introduction

Tuberous sclerosis (TSC) is a genetic, multisystemic disorder characterised by widespread hamartomas with cerebral, cardiac, cutaneous, ocular, renal, pulmonary, and hepatic involvement [1,2]. The disorder has a birth incidence of 1:6000 [3].

TSC has an autosomal dominant pattern of inheritance, although two-thirds of all cases result from sporadic mutations. Multigenerational family analysis of

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Abbreviations: AML, liver angiomyolipoma; TSC, tuberous sclerosis.

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linkage resulted in mapping *TSC1* and *TSC2* genes [4,5] encoding, respectively, for hamartin and tuberin.

The hamartin–tuberin complex inhibits the mammalian target of rapamycin (mTOR) that controls cell growth and proliferation. mTOR detects signal of nutrient availability, hypoxia or growth factor stimulation [6,7]. This pathway is activated by estrogens (17β-estradiol), via tuberin and the small GTPase Ras homologue, thus explaining the greater predisposition to tumours in women than in men [8].

Multiple, bilateral angiomyolipomas are the most common renal finding appearing in about 70–90% of adult patients, and are more often symptomatic in women [9,10]. They are composed of abnormal blood vessels, smooth muscle and adipose tissue, and have an immunoreactivity for HMB-45 (Human Melanoma Black). Occasionally angiomyolipomas may involve the liver, yet multiple hepatic lesions are extremely rare and usually seen in patients with fully expressed TSC [11,12]. We report on a female patient with TSC and massive multiple liver and renal angiomyolipomas, who experienced a remarkable clinical improvement with long-term tamoxifen treatment, associated with tumour size reduction and improved quality of life.

2. Case history

A 26-year-old female with a clinical and molecular diagnosis of TSC was admitted in June 2005 to the Liver Unit for severe malnutrition, anorexia, nausea, and abdominal pain. At the age of two years the patient experienced generalized seizures and a clinical diagnosis of tuberous sclerosis was made, in the presence of cerebral, renal, and hepatic involvement. DNA testing confirmed the mutation on chromosome 16 (exon 39). An anti-epileptic treatment with vigabatrin was administered with seizure remission until 12 years of age, when focal motor seizures appeared. Lamotrigine and successively levetiracetam were started with partial seizure control. Brain MRI showed cortical tubers, multiple subependymal nodules, giant cell astrocytoma, radial bands, and multiple cystic areas on the white matter. The IQ value was normal, and awake and sleep EEG recordings did not reveal epileptic abnormalities.

At that time the patient experienced nausea, anorexia, epigastric pain and severe malnutrition. When she was 22 years old, her quality of life progressively worsened and at the age of 26 she was referred to our hospital for a clinical evaluation.

Abdominal MRI showed multiple diffuse angiomyolipomas and cystic formations in both kidneys. The liver was grossly enlarged (longitudinal diameter = 30 cm), with the left lobe occupying the mid and left abdomen, causing severe gastric compression. T1-weighted dynamic sequences after gadolinium administration showed multiple, nodular, hypointense and non-homogeneous lesions of different sizes. The largest one (diameter = 12 cm) was located between segment VII and VIII (Fig. 1, panel A). Echo-guided percutaneous liver biopsy revealed tumoral tissue with microscopic and ultrastructural features of angiomyolipoma. Upper gastrointestinal endoscopy disclosed a surface gastritis associated with two inflammatory polyps in the stomach.

The patient's body weight was 50 kg, body mass index was 19 and waist abdominal circumference was 90 cm. All liver function tests were repeatedly normal.

Neither previous pregnancies nor estrogen replacement therapy were reported. An oral treatment with tamoxifen, an anti-estrogen drug, was started (20 mg b.i.d). After 3 months of treatment, the patient experienced a significantly improved quality of life associated

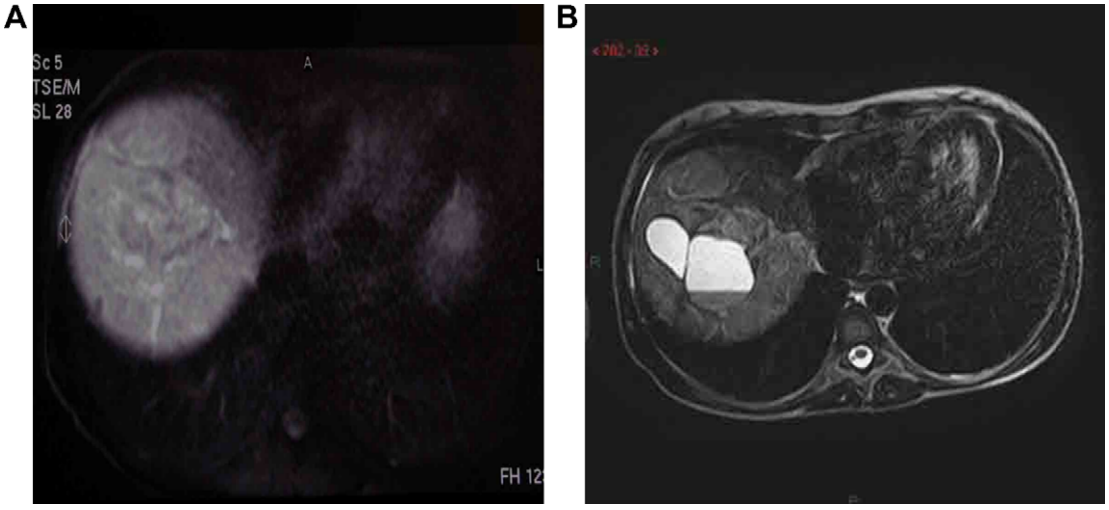

Fig. 1. T2-weighted axial MRI of the upper abdomen performed before starting tamoxifen showing a large focal area between liver segments VII and VIII (A); axial MRI, performed after 12 months of tamoxifen treatment, revealing a significant reduction of the largest lesion with an enlarged liquid central area (B). [This figure appears in colour on the web].

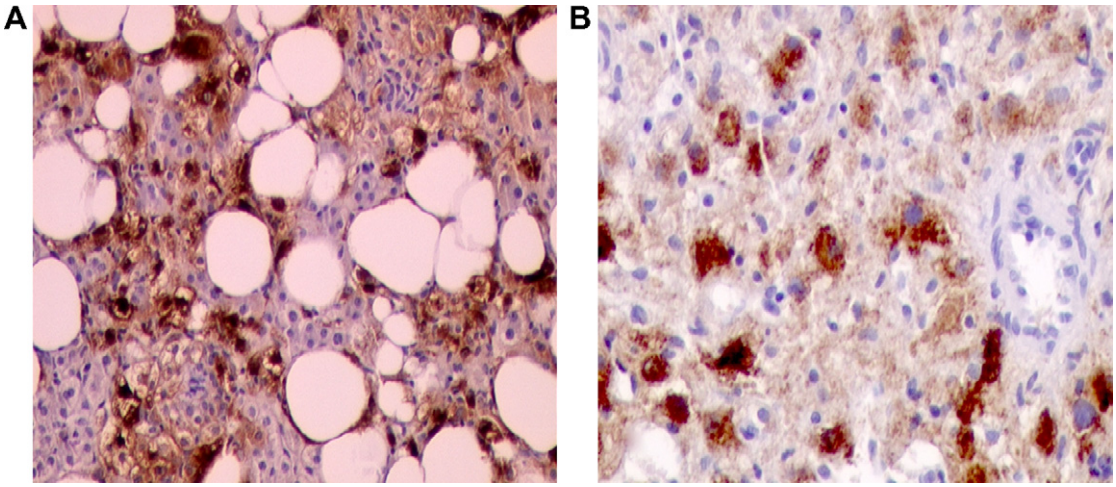

Fig. 2. Eosinophilic epithelioid cells with focal nuclear positivity for estrogen receptors (ER) (A); cytoplasmic granular positivity for HMB45. Eosinophilic epithelioid cells positive for vimentin and smooth muscle actin (B). [This figure appears in colour on the web].

with a slight weight gain. A further liver MRI showed volumetric reduction of many hepatic lesions. Therefore, oral tamoxifen was continued at the same dose without interruption. After 6 months of treatment, weight gain was 4 kg, and clinical conditions continued to improve, with the recovery of well-being and appetite. After 12 months of treatment, weight increase was 6 kg and waist abdominal circumference was reduced from 90 to 83 cm. Abdominal MRI control revealed a significant reduction of the largest lesion, with an enlarged liquid central area (Fig. 1, panel B). Moreover, liver size and stomach compression were reduced due to fewer and smaller liver lesions. Neither cerebral lesions nor renal angiomyolipomas were significantly improved.

3. Histological analysis

Histological analysis was performed in formalin-fixed, paraffin-embedded liver biopsy tissue by conventional methods. The liver showed diffuse infiltration by clusters of smooth-like muscle cells, numerous scattered adipocytes, often grouped, thick-walled blood vessels and capillaries, associated to inflammatory cells, including small lymphocytes, plasma cells, and histiocytes.

The smooth-like muscle cells consisted of spindle-shaped cells or larger rounded cells with clear cytoplasm and eosinophilic epithelioid cells. The immunohistochemical analysis was performed in 4–6 μm sections of liver biopsy specimens, using the avidin–biotin complex (ABC) method. Angiomyolipoma spindle, rounded and epitheliod cells were positive for smooth muscle actin (Dako) and vimentin (Dako). Adipose cells were positive for S-100 protein (Dako). Pancytocheratin were negative. The estrogen (ER) and progesterone (PR) receptor analysis was performed using monoclonal antibody against ER (mouse anti-human estrogen receptor, clone 1D5-IgG1, Ylem) and PR (mouse anti-human progesterone receptor, clone 1A6-IgG1, Ylem), showing ER nuclear positivity focally restricted to angiomyolipoma epithelioid and clear cells (Fig. 2, panel A), and PR negativity. Liver sections were also investigated for the presence of HMB45 reactivity (Mouse anti-human melanosome, clone HMB45, isotype IgG1 Kappa, Dako) (Fig. 2, panel B).

4. Discussion

As the incidence of TSC-related lesions increases with age, hepatic hamartomas are more common in adults, being reported in 23–45% of cases [13,14] with a higher frequency in females. They do not usually cause hepatic dysfunctions, and are mostly found incidentally or during periodic follow-up studies. Only few symptomatic hepatic hamartomas have been reported, presenting with flank pain, spontaneous haemorrhage or rapid growth [15,16]. In contrast to renal lesions, hepatic angiomyolipomas grow more slowly and are not mentioned as a possible cause of death in TSC patients [17].

Nowadays, the pathogenesis of angiomyolipomas is still nearly unknown and, currently, no specific pharmacological treatments have been reported. A beneficial effect of rapamycin on renal angiomyolipomas [18,19] and subependymal giant cell astrocytomas [20] has been reported in several studies, suggesting that rapamycin (an inhibitor of mTOR pathway) or its analogues may be effective in the treatment of various TSC manifestations: e.g., lymphangioleiomyomatosis [21], renal angiomyolipomas [22], renal cell carcinoma [23], or even in reversing polycystic kidney disease [24].

Recently, El-Hashemite et al. [25], through analysis of $Tsc1^{+/-}$ mice, proved the importance of estrogen

signaling *in vivo* for the growth of TSC lesions, suggesting possible benefits of tamoxifen therapy in angiomyolipomas and lymphangioleiomyomatosis.

These experimental observations prompted us to explore in our young patient the clinical effectiveness of tamoxifen, a widely used drug in humans for the prevention and the treatment of estrogen-related cancer with few side-effects.

The patient, initially referred to evaluate the possibility of partial hepatic resection, due to the high degree of gastric compression, showed significant clinical improvement in terms of nutritional status and quality of life, already evident after the initial months of treatment. This improvement became remarkable and sustained over time, with reduced size of liver angiomyolipomas, including their partial necrotic involution, and until now has delayed surgical intervention. Since in the literature tamoxifen has been reported to cause steatohepatitis [26,27], a close monitoring of liver function tests and routine ultrasounds are constantly required.

This is to our knowledge the first report in which tamoxifen has been successfully used in a TSC patient with multiple liver angiomyolipomas.

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