

## Tuberous Sclerosis with Multiple Unusual Associations

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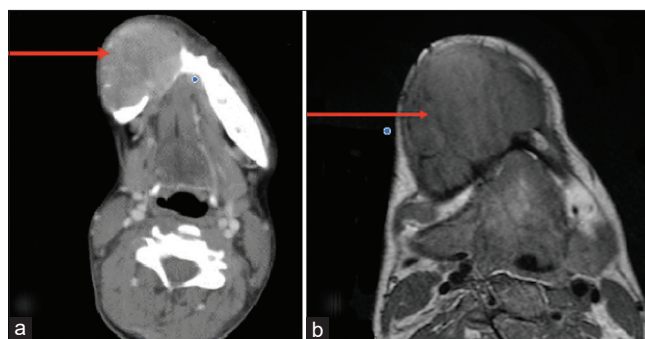
Tuberous sclerosis complex (TSC) is a multisystemic condition cardinally characterized by the triad of epilepsy, facial angiofibromas, and cognitive impairment.<sup>[1]</sup> The association with tumors is well known, including cardiac rhabdomyoma, lymphangioliomyomatosis, angiomyolipomas, retinal hamartomas, and the dreaded subependymal giant cell astrocytoma.<sup>[1]</sup> Less commonly described tumors include chordomas and desmoplastic fibromas (DFs). We have previously described in our patient an uncommon association of Sturge–Weber-like intracranial calcifications in combination with TSC.<sup>[2]</sup> We now report the first case of the occurrence of mandibular myxofibrosarcoma in this patient, adding the diverse unusual features in this case.

A 10-year-old female had initially presented to us with refractory epilepsy with onset from 6 months of age. She had global developmental delay as well as significant language and hearing impairment. She was third-born to a nonconsanguineous couple with no family history of neurological complaints. Antenatal and perinatal period had been unremarkable. Examination revealed microcephaly (head circumference <3 SD). She had profound mental retardation (intelligence quotient 20). She had multiple contractures of ankles, knees and elbows, right hemiparesis, and hearing impairment. Cutaneous examination revealed multiple ash leaf macules, Shagreen patch and facial angiofibromas, lumbosacral midline hair tuft, and high-arched palate. Computed tomography brain showed cerebral atrophy and gyral calcifications in left temporo-parieto-occipital region and multiple calcific foci in subependymal location along with bilateral lateral ventricles. MRI brain showed absent cortical tubers, enlarged choroid plexus, or leptomeningeal angiomas and the presence of extensive gyral calcification and calcified subependymal nodule. Genetic analysis showed a heterozygous mutation in exon 18 of *TSC* type 1 gene.<sup>[2]</sup>

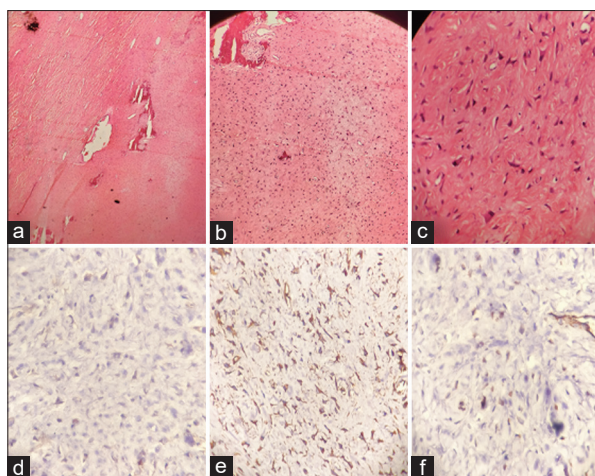
The child was lost to follow-up and presented again to us at 17 years of age with bleeding from a mandibular swelling for 2 days. The child had significant developmental delay and had been largely bedridden. She could sit with support only

and had further developed contractures of fingers. She also had not experienced any gain in language domain or in any developmental milestones over the past 7 years. The child had regular menstrual cycles, which started at 11 years of age. However, she had poorly developed breasts, with only small amounts of glandular tissue with poorly developed areola. She had no axillary or pubic hair growth.

She had developed a slowly increasing mandibular swelling for the past 1.5 years. Additionally, she had also developed a swelling in the right breast of unclear duration. Contrast-enhanced CT of mandible showed a large expansile lytic lesion in right half of body of mandible involving the entire thickness of alveolar arch with marked cortical thinning and loss of ipsilateral canine tooth. Lesion showed some enhancing soft tissue along with few bony septae, no matrix mineralization, and narrow zone of transition. On T1-weighted MR images, lesion showed intermediate signal intensity with hypointense areas within, and on T2-weighted images, hypointense lesion with few focal hyperintense areas was seen [Figure 1]. Fine-needle aspiration cytology (FNAC) of the mandibular swelling had been done on outpatient basis 1 year back and was suggestive of DF. Excisional biopsy



**Figure 1:** (a) Contrast-enhanced CT of the mandible showing (red arrow) a large well marginated expansile lytic lesion with enhancing soft tissue in the right half of body of mandible; (b) T1-weighted MRI of the mandible showing (red arrow) intermediate signal intensity lobulated lesion along with few hypointense areas within



**Figure 2:** Histopathology of myxofibrosarcoma. (a) 4×, (b) 10×, (c) stellate-shaped macrophages seen, (d) CD99 focal positivity, (e) vimentin positivity, and (f) smooth muscle actin (SMA) positivity

of the breast mass showed fibroadenoma. She underwent excisional biopsy of the mandibular tumor.

Due to progressive growth of the swelling, she had developed malocclusion, which led to bleeding from the oral aspect of the growth because of injury. She was taken up for simultaneous excision of the breast mass, mandibular resection, and reconstruction. She was intubated without significant difficulty. The skin and subcutaneous tissue were free from mass and there was no invasion of intraoral structures. Mandibular resection was performed taking a 1-cm margin; the defect crossed midline and reached till ramous on right side. Reconstruction was performed.

Histopathology revealed the presence of myxofibrosarcoma [Figure 2]. She needed to undergo postoperative tracheostomy and mechanical ventilation. She developed nosocomial pneumonia and succumbed on the seventh postoperative day. Autopsy was not performed as her parents were unwilling for the same.

TSC is a rare autosomal dominant disorder resulting from mutations in TSC1 or TSC2 tumor suppressor genes. TSC patients exhibit overactivity in the mammalian target of rapamycin (mTOR) pathway predisposing to abnormal proliferation and development of intracranial (Sub-Ependymal Giant cell Astrocytoma (SEGA)) as well as extracranial tumors in the heart, kidney, lungs, and skin.

The initially performed FNAC from the jaw tumor in our patient reported DF. DF represents an intraoral manifestations of the multisystem disorder.<sup>[3]</sup> The tumor has a tendency to form proliferative fibroblastic hamartomas and attains a mean size of about 40 mm.<sup>[4]</sup> Six cases of DF associated with TS have been reported in literature.<sup>[3-8]</sup> Tumor resection or alternately, aggressive curettage is used for management along with mTOR inhibitors. However, excisional biopsy in our patient revealed finally myxofibrosarcoma of the mandible, suggesting that initial FNAC sample was likely not representative of the tumor. This is a rare soft tissue sarcoma (<5%) with a locally

infiltrative nature. It has not been reported in association with TSC so far. It is an aggressive tumor with a high recurrence rate. Treatment involves en bloc resection of tumor with a wide margin followed by reconstruction, which our patient underwent. There is one previous case report of a gingival myxofibroma in an 8-year-old tuberous sclerosis patient.<sup>[9]</sup> In myxofibrosarcoma, amplifications of chromosome 5p (such as rapamycin-insensitive binding partner of mTOR) and 1p/1q and deletions of tumor-suppressor genes, including *CDKN2A/B* and *TP53*, have been reported.<sup>[10]</sup> These may explain the interrelation with TSC.

Additional unusual features were present in our patient. She had regular menstrual cycles with menarche at 11 years of age. However, she had poorly developed breasts, and no axillary or pubic hair growth. Ultrasonography pelvis was normal and levels of luteinizing hormone, follicle stimulating hormone, and estradiol were also within normal ranges, giving us no explanation for the pubertal oddity. Our patient also had breast fibroadenomas. According to a Japanese study of 166 TSC patients, around 95 patients were screened for endocrinal issues, of which only 6 had some form of mammary tumors.<sup>[11]</sup> Moreover, she had severe intellectual disability. Intellectual impairment may be present in up to 40% of patients with TSC, but severe intellectual impairment as exhibited by our patients is unusual (seen in only around 3.6% patients in the Japanese series).<sup>[11]</sup> We have already reported the radiological rarity of overlapping radiological features between Sturge–Weber syndrome and TSC.<sup>[2]</sup>

Our case highlights multiple unusual and multisystemic associations in patients with TSC. Additionally, it expands the already wide neoplastic spectrum connected with TSC to include myxofibrosarcoma, a locally aggressive form of soft tissue sarcoma.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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**Submitted:** 07-Apr-2020 **Revised:** 06-May-2020 **Accepted:** 07-May-2020

**Published:** 08-Jul-2020

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**DOI:** 10.4103/aian.AIAN\_266\_20