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Primary Cutaneous Leiomyosarcoma Arising in a Patient With Li-Fraumeni Syndrome: A Neoplasm With Unusual Histopathologic Features and Loss of Heterozygosity at TP53 Gene

To the Editor:

Li-Fraumeni syndrome (LFS) is an inherited cancer predisposition syndrome characterized by sarcomas in children and young adults, early-onset breast cancer, brain tumors, adrenal cortical carcinoma, and leukemia.[1] In patients with this syndrome, several cutaneous neoplasias have been described such as multiple primary cutaneous melanomas,[2] atypical fibrous histiocytoma,[3] sebaceous carcinoma,[4] infantile cutaneous rhabdomyosarcoma,[5] and atypical fibroxanthoma.[6]

We report here the first cutaneous pilar-type leiomyosarcoma (LMS) arising in a patient with classic LFS. This tumor showed a plexiform growth pattern and similar areas to a symplastic pilar leiomyoma. Tumor analysis by Next-Generation Sequencing detected loss of heterozygosity (LOH) at TP53 gene.

The authors declare no conflicts of interest.

CASE REPORT

A 32-year-old woman developed a 15-mm reddish nodular lesion on her right arm with bleeding signs on the surface (Fig. 1A). At the age of 28, she was diagnosed with a ductal carcinoma in situ in the right breast. She belonged to a family associated with LFS, being a carrier of a germline TP53 gene mutation denoted as c.365_366delTG (V122 fs*26).

The skin lesion was excised with free margins. Histopathological examination showed a multinodular tumor confined to the dermis with no extension into the subcutaneous fat and covered by hyperplastic epidermis (Fig. 1B). The tumor was composed of multiple nodules of spindle cells separated by stroma, adopting a plexiform pattern (Fig. 1C). Most tumor nodules showed spindle cells with plump, cigar-shaped nuclei, and eosinophilic cytoplasm, and they were arranged in fascicles on a myxoid stroma (Fig. 1D). Some cells showed certain pleomorphism and nuclear hyperchromatism, whereas others seemed to originate from hypertrophic muscle bundles of arrector pili (Fig. 2A).

There was no mitosis or necrosis, but these areas resembled a symplastic pilar leiomyoma. In other nodules, the neoplastic cells showed marked atypia, pleomorphism, and multinucleation (Fig. 2B). There was no necrosis but the mitotic activity was 6 per 10 high-power field. Atypical mitotic figures were noted.

Immunohistochemical study revealed that neoplastic cells were strongly positive for smooth muscle actin, desmin, and h-caldesmon (Fig. 2C) but negative for cytokeratin AE1/3, S-100, HMB-45, c-Kit (CD117), epidermal growth factor receptor, and p53. More than 90% of neoplastic cells showed nuclear staining for Ki-67 (Fig. 2D). According to the histopathological findings of this tumor, a diagnosis of pilar-type LMS was rendered.

Next-Generation Sequencing was performed on the paraffin-embedded tissue, using the TruSight Tumor 26 gene panel (Illumina) on a MiSeq sequencer (Illumina). Identification of somatic mutations was performed on a tumor sample with a purity of tumor cells 90%. Table 1 shows the evaluated genes and the genetic polymorphisms found in this LMS. In the case of TP53, the mutation c.365_366delTG (V122 fs*26) was identified in 88% of the tumor analyzed sequences with coverage of 13.164 sequences, which together with rs1042522 G/C in 10% and C/C in 90% of tumor cells suggested LOH at TP53 gene.

DISCUSSION

Primary cutaneous LMS is a malignant smooth muscle tumor, essentially confined to the dermis with or without minimal involvement of the subcutis. Microscopically, it can display a fasciculated, pilar-type or pleomorphic architectural pattern.[7] However, a plexiform pattern has not been described in the LMS. This unique growth pattern is characterized by multiple tumoral nodules each composed of neoplastic cells with intervening stroma between the nodules. The plexiform pattern is usually associated with complex multinodular lesions of neural, melanocytic, and fibrohistiocytic origin[8] and sometimes it indicates an underlying disease. This is the case of the plexiform neurofibroma that is pathognomonic of the neurofibromatosis type I. We do not know the relevance of the plexiform pattern in this tumor, but we believe that pilar-type LMS should be included in the histopathological differential diagnosis of skin plexiform lesions.

Fons et al[9] have described a cutaneous LMS originating in a symplastic pilar leiomyoma pointing out that it can be a potential diagnostic pitfall. In our case, the presence of similar areas to a symplastic pilar leiomyoma raised the possibility that LMS arose from a precursor. However, the presence of the somatic mutation TP53 V122 fs*26 in 90% of neoplastic cells along with a high Ki-67 rate throughout the tumor suggests that symplastic pilar leiomyoma areas really are symplastic leiomyoma–like LMS.

The occurrence of familial sarcoma is the basis of the clinical definition of the LFS. The patients with this syndrome have a lifelong risk of developing several sarcoma types. The underlying genetic defect is found in a germline mutation in the TP53 tumor-suppressor gene.[10]

We report in this cutaneous pilar-type LMS, the somatic mutation TP53 c.365_366delTG at the cDNA level and p.Val122AspfsX26 at the protein level.

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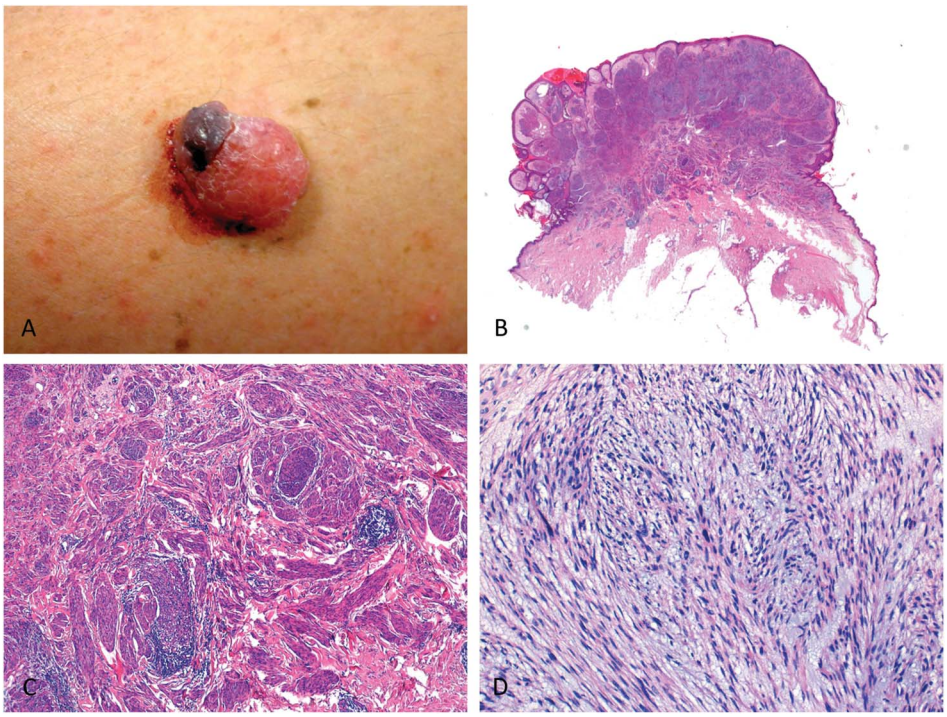

FIGURE 1. A, Reddish nodular lesion on her right arm showing bleeding on the surface. B, Scanning magnification shows a multinodular tumor occupying the entire dermis covered by hyperplastic epidermis (HE ×2). C, Leiomyosarcoma with plexiform pattern (HE ×10). D, Fascicles of spindle cells some of which show nuclear hyperchromatism and pleomorphism (HE ×20). HE, hematoxylin and eosin.

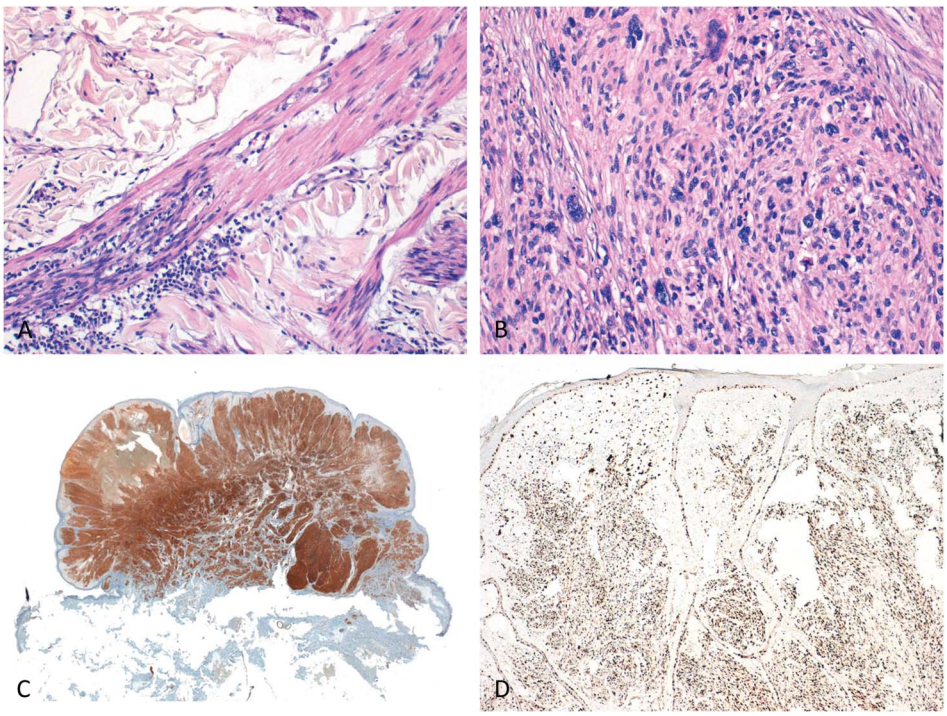

FIGURE 2. A, Spindle cells originating from a hypertrophic arrector pili with lymphocytic infiltrate (HE ×10). B, Tumor cells showing nuclear pleomorphism, multinucleation, and atypical mitotic figures (HE ×40). C, Immunohistochemistry for h-caldesmon in the tumor cells (×2). D, Ki-67 immunostaining in more than 90% of the tumor cells (×10). HE, hematoxylin and eosin.

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TABLE 1. Genes Evaluated and Genetic Polymorphisms Found in the Primary Cutaneous Pilar-Type Leiomyosarcoma

Gene Sequencing Panel	Genetic Polymorphisms
AKT1 ALK APC BRAF CDH1	rs41115 (A/A) in APC
CTNNB1 EGFR ERBB2 FBXW7	rs1050171 (G/A) in EGFR
FGFR2 FOXL2 GNAQ GNAS KIT	rs55789615 (C/T) in KIT
KRAS MAP2K1 MET MSH6 NRAS	rs1873778 (G/G) in PDGFRA
PDGFRA PIK3CA PTEN SMAD4 SRC	rs2228230 (C/T) in PDGFRA
STK11 TP53	rs1042522 (G/C) and (C/C) in TP53

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Deletion of TG bases causes a frameshift, which changes a Valine to an Aspartic Acid at codon 122 in exon 4, and creates a premature stop codon at position 26 of the new reading frame. This mutation is pathogenic, it causes loss of normal protein function and it is indicative of LFS. In addition, rs1042522 CC in 90% of the TP53 sequences indicates LOH, namely, the neoplastic cells have inherited a mutated allele and malignancy develops when the second copy of TP53 or wild-type allele is lost by deletion affecting the entire gene.

Ognjanovic et al[11] have studied the sarcomas in the TP53 germline mutation carriers suggesting a relationship between the mutation type and the age at onset and type of sarcoma. The mutations associated with sarcomas occurring under the age of 20 (rhabdomyosarcoma and osteosarcoma) are often missense mutations in the DNA-binding domain of p53 protein. However, the mutations associated with sarcomas that appear after the age of 20 (liposarcoma and LMS) are mutations that deleted the whole p53 protein or missense mutations outside of DNA-binding motifs. In our case, although the mutation occurs in the DNA-binding domain, at codon 122 of p53 protein, it is a mutation that deleted the whole p53 protein. This would explain the appearance of LMS in the patient at the age of 32.

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Hydroa Vacciniforme-Like Cutaneous T-Cell Lymphoma in an Adult Presenting With Facial Edema and Recurrent Oral Ulceration

To the Editor:

Hydroa vacciniforme–like cutaneous T-cell lymphoma (HVTCL) is an Epstein–Barr virus (EBV)-associated lymphoma affecting mostly children in Latin America and Asia.[1] Clinical manifestations are similar to those with HV. Eruptions may be polymorphous (eg, erythema, blisters, papulovesicles, and ulcers) with edema on the face, periorbital area, or lips. Patients may have recurrent skin lesions in sun-exposed and non–sun-exposed areas, accompanied by systemic symptoms. Herein, we report, for the first time, an adult presenting with facial edema and recurrent oral ulceration.

The patient was a 48-year-old man referred to the outpatient department of our hospital. Seven months earlier, he had suffered from repeated oral ulceration accompanied by pain, dysphagia, and hoarseness. Six months earlier, symmetric erythema and edema appeared on the face (especially on the eyelids).

Biopsy of an oral ulcer was undertaken, and a diagnosis of acute laryngitis and sensitization dermatitis made at a local hospital. Antibiotics and antiallergic treatments were administered. All the symptoms mentioned above disappeared after several weeks. Then, these symptoms recurred and the patient was admitted to our hospital.

Physical examination revealed systematic erythema and edema on the face, especially on the upper eyelids (Fig. 1A). Several ulcers with overlying

The authors declare no conflicts of interest.

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