Dear Editors,

A 57-year-old female patient with a previously known history of Schimmelpenning-Feuerstein-Mims syndrome (SFMS) presented to our department for evaluation of multiple epitheliomas. Her decades-long medical history included multiple benign and malignant cutaneous neoplasms including basal cell carcinoma, squamous cell carcinoma, Bowen’s disease (Figure 1), syringocystadenoma papilliferum, sebaceoma (Figure 1), poroma and trichoblastoma. Since childhood, she had also suffered from vitamin D-resistant hypophosphatemic rickets, which had resulted in significant growth retardation, asthenia, myopathic symptoms and severe orthopedic deformities. Neurological examination showed left-sided hypoglossal nerve palsy and left-sided hypoacusis. The patient’s mental and cognitive development had been normal. There were no other neurological or ophthalmological abnormalities. The family history was negative with regard to genodermatoses.

Clinical examination showed a large congenital, sharply demarcated, linear nevus sebaceus with multiple coalescing papillomatous and verrucous areas. The lesion followed the lines of Blaschko and affected the head, face, arm and trunk on the left side of the body (Figure 1, left side of the body). In addition, there was a large, sharply demarcated café-au-lait spot with typical areas of macular hyperpigmentation (nevus spilus) that involved the head, face, trunk and arms on the right side of the body (Figure 1, right side of the body).

High-coverage molecular genetic testing revealed the heterozygous p.Gly13Arg mutation in about 3% of alleles in the HRAS gene in fibroblast DNA from affected tissue. This is a known mutation that leads to activation of the RAS-MAPK signaling pathway. The fact that this mutation was not found in the DNA from the patient’s blood confirmed the diagnosis of a mosaic RASopathy (SFMS). No pathogenic mutations were found in the FGFR23, GNAS, KRAS and NRAS genes.

SFMS is a rare sporadic hereditary phakomatosis with variable expressivity. Clinically, it may present with multiple malformations and dysplasias affecting the skin (including nevus sebaceus, multiple benign and malignant tumors), the eyes (including divergent strabismus, corneal opacities, xanthelasmas), the brain (including mental retardation, cerebral seizures, hydrocephalus, cranial asymmetries), the skeleton (including disproportionate small stature, scoliosis) and the heart [1, 2].

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Figure 1  Erythematous, nodular, hyperkeratotic erosive tumor with telangiectasias in the left retroauricular area; the lesion has developed within a brownish-yellow plaque with a soft, verrucous texture (a). Multiple erythematous, hyperkeratotic, partially crusted plaques, each measuring approximately 5 mm in diameter (b). Nevoid, sharply demarcated lesion primarily affecting the left side of the thorax; the lesion follows the lines of Blaschko and is marked by multiple confluent papillomatous and verrucous areas. Prominent coalescence of such verrucous areas along the midline (left side of the body). Large café-au-lait spot-like lesion affecting the right side of the thorax; the lesions is covered with scattered, more darkly pigmented macules (right side of the body); ventral aspect of the body (c); dorsal aspect of the body (d).
SFMS is caused by postzygotic gain-of-function mutations (somatic mosaicism) in the RAS genes of the RAS-MAPK-PI3K/AKT signaling pathway [3]. In the vast majority of cases, HRAS (approximately 95%) and KRAS (approximately 5%) mutations have been reported, whereas NRAS mutations (< 1%) are much more uncommon [2, 3]. The mutation detected in our patient has previously been found in individuals with epidermal nevi as well as patients with SFMS [2]. Thus, SFMS represents a mosaic RASopathy [1, 4].

Characteristic of SFMS, nevus sebaceous lesions are considered facultative precancerous lesions, given that a number of benign and malignant neoplasms have been shown to arise therefrom [5, 6].

The most common benign tumors are syringocystadenoma papilliferum (occurring in up to 20% of patients) and trichoblastoma [1, 5, 6]. The most common malignancy is basal cell carcinoma, with a prevalence of less than 1% [1, 2, 6]. Squamous cell carcinomas are more uncommon [1, 4]. SCALP syndrome is an important differential diagnosis [7].

As in our patient, SFMS is not infrequently associated with vitamin D-resistant hypophosphatemic rickets, which is thought to cause growth retardation, skeletal deformities, progressive asthenia and myopathic symptoms [1]. The condition is referred to as cutaneous skeletal hypophosphatemia syndrome (CSHS) [8]. As the aforementioned CSHS-related symptoms are mediated by FGF23, treatment with anti-FGF23 antibodies may be a useful approach [8].

There is currently no curative treatment for SFMS [1, 6]. Depending on the organ system primarily affected, interdisciplinary management is required, with dermatologists usually playing a central role. Given the significantly increased risk of various cutaneous neoplasms arising from nevus sebaceous lesions, close dermatological follow-up is particularly important.

Conflict of interest
None.

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