CLINICAL PHENOTYPIC SPECTRUM OF SCHIMMELPENNING–FEUERSTEIN–MIMS SYNDROME

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Abbreviations: CSHS = cutaneous-skeletal hypophosphatemia syndrome; SFMS = Schimmelpenning-Feuerstein-Mims syndrome.

Case report. A 5-year-old boy presented for evaluation of cutaneous and skeletal lesions. He exhibited an extensive linear epidermal nevus involving the scalp, the right upper and lower limbs, and the trunk predominantly on the right side, with hyperpigmented, verrucous plaques distributed along the lines of Blaschko (Figs. 1, 2).

The skeletal examination revealed asymmetry of the upper limbs, with apparent hemihypertrophy of the right side. Chest radiography showed rib asymmetry (Fig. 3). Radiographs of the limbs (Figs. 4, 5) demonstrated asymmetry, dysplasia of the metacarpals and phalanges, and cupping and widening of the metaphyses, more severe on the right side.

Histologic examination of a cutaneous lesion showed features consistent with an organoid epidermal nevus.

Laboratory investigations revealed a serum phosphorus level of 1.8 mg/dL (0.58 mmol/L), reduced compared with the pediatric reference range of 2.5-5.0 mg/dL (0.81-1.62 mmol/L), with age-specific normal values of 1.19-1.74 mmol/L. Serum calcium levels remained within normal limits. Vitamin B12 was 568.60 pg/mL (nr 190-900). The 25-hydroxyvitamin D level was 29.89 ng/mL, ruling out nutritional vitamin D deficiency as a causative factor. Thyroid function tests showed FT3 6.90 pmol/L (vn 3,10-6,80), FT4 15.90 pmol/L (nr 12,00-22,00), and TSH 2.80 µIU/mL (0,27-4,20), all within normal limits. The profound hypophosphatemia (64% below the age-adjusted lower limit), in the presence of preserved renal function, was pathognomonic of FGF23-mediated phosphate wasting, characteristic of cutaneous-skeletal hypophosphatemia syndrome in the context of SFMS.

Oral phosphate supplementation at 40 mg/kg/day, divided into five daily doses, and calcitriol at 0.25 µg/day were administered. Due to persistent hypophosphatemia, rescue therapy with high-dose intramuscular vitamin D (600,000 IU) was planned.

Fig. 1:

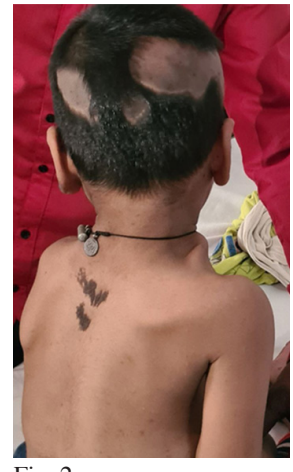

Fig. 2:

Fig. 1, 2: Extensive linear nevus sebaceous involving the scalp and back of the neck following the lines of Blaschko.

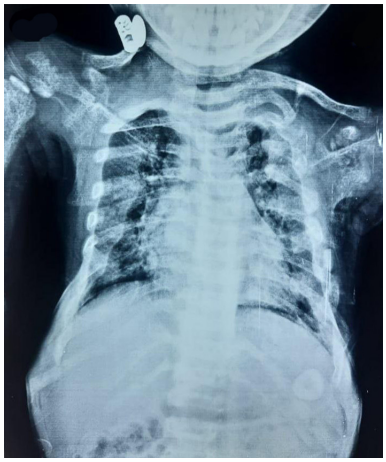

Fig. 3:

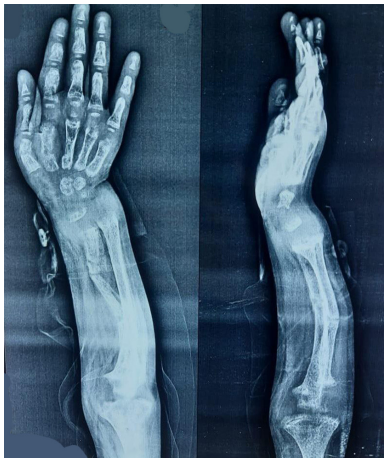

Fig. 4:

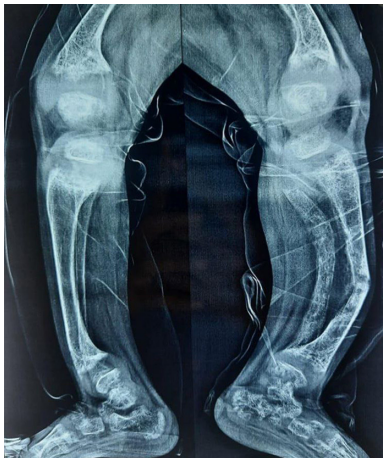

Fig. 5:

Fig. 3, 4, 5: Chest radiograph with rib asymmetry (Fig. 3). Limb radiographs (Figs. 4, 5) show asymmetry, with greater severity on the right; dysplasia of the metacarpals and phalanges, with cup-shaped widening of the metaphyses.

Discussion. A 68-year synthesis of the literature defines Schimmelpenning-Feuerstein-Mims syndrome (SFMS) as a mosaic RASopathy, necessitating a paradigm shift from the traditional "classic triad" to a modular diagnostic framework. Our analysis suggests that diagnosis should be based on the presence of an epidermal-sebaceous nevus in association with neurologic, ocular, or skeletal abnormalities. The historically emphasized triad (nevus, seizures, and intellectual disability) likely reflects selection bias toward more severe phenotypes rather than biological reality, as it is absent in the majority of patients in this cohort. SFMS is currently best regarded as a pathological clinical phenotype within the broader spectrum of epidermal nevus syndromes.

A critical finding of this review is the correction of oncologic risk estimates. Historical reports suggesting a 10-20% risk of pediatric basal cell carcinoma were largely attributable to histopathologic misclassification of benign trichoblastomas. Contemporary molecular and longitudinal evidence indicates that the true risk of malignancy in childhood is <1%. Consequently, routine prophylactic excision of sebaceous nevi is not clinically indicated; management should prioritize longitudinal surveillance, reserving surgical intervention for cosmetic indications or suspicious lesions arising in adulthood (8, 19).

Our data identify a distinct metabolic subgroup (5-15%) characterized by FGF23-mediated hypophosphatemic rickets, representing the extreme end of cutaneous-skeletal hypophosphatemia syndrome (CSHS) within the SFMS spectrum. Distinguishing vitamin D deficiency from vitamin D resistance is critical; the latter, observed in SFMS, results from impaired activation rather than substrate deficiency. Accordingly, standard cholecalciferol supplementation is ineffective. Optimal management requires active vitamin D metabolites (calcitriol) or targeted FGF23 blockade – burosumab – (22, 24).

The relationship between normophosphatemic and hypophosphatemic variants appears to represent a phenotypic continuum rather than a binary classification. This is supported by identification of identical somatic mutations – particularly HRAS G13R – in both subgroups and by a continuous distribution of serum phosphate levels. The emergence of CSHS likely reflects the extent and timing of mosaicism within osteocytic lineages. We recommend routine phosphate screening in all SFMS patients with skeletal involvement to detect subclinical metabolic abnormalities (25, 27).

SFMS must be rigorously distinguished from other mosaic neurocutaneous syndromes to ensure appropriate surveillance. Although both SFMS and neurofibromatosis type 1 (NF1) involve the RAS signaling pathway and share neurologic and skeletal manifestations, NF1 is a germline autosomal dominant disorder with a substantially higher risk of neural tumors. Similarly, although Sturge–Weber

syndrome shares mosaic inheritance and ipsilateral neurologic deficits, its defining cutaneous feature is a capillary malformation ("port-wine stain") driven by somatic GNAQ mutations, whereas SFMS is defined by a RAS-driven epidermal nevus.

Molecular confirmation remains the diagnostic gold standard, particularly via biopsy of the affected skin. Clinicians should be aware that peripheral blood testing is frequently negative, as variant allele frequency in leukocytes often falls below the detection threshold due to the localized nature of somatic mosaicism.

Future research should transition from retrospective syntheses to prospective, multicenter longitudinal cohorts to define the true incidence of systemic manifestations and age-related complications. Validation of genotype–phenotype correlations – particularly KRAS with CNS/ocular involvement and HRAS with skeletal disease – represents a priority requiring large-scale molecular characterization.

Therapeutically, randomized controlled trials comparing conventional calcitriol-based regimens with burosumab are needed, particularly in resource-limited settings where cost-effectiveness is paramount. Pharmacokinetic studies should define optimal dosing strategies for intramuscular vitamin D. Additionally, the potential use of targeted MEK or PI3K inhibitors for refractory epilepsy or progressive skeletal dysplasia warrants exploration in high-risk, molecularly confirmed cases.

Conclusions. Schimmelpenning-Feuerstein-Mims syndrome is a clinically and genetically heterogeneous neurocutaneous disorder resulting from postzygotic mutations of the RAS signaling pathway.

Early recognition of the pathognomonic epidermal sebaceous nevus should prompt systematic multidisciplinary evaluation, enabling anticipatory management of potential neurologic, ophthalmologic, and metabolic complications.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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References

1) Schimmelpenning GW. Clinical contribution to symptomatology of phacomatosis. *Fortschr Geb Rontgenstr Nuklearmed*. 1957;87(6):716-20.
2) Feuerstein RC, Mims LC. Linear nevus sebaceus with convulsions and mental retardation. *Am J Dis Child*. 1962;104:675-9.
3) Mitchell BJ, Rogers GF, Wood BC. A patient with Schimmelpenning syndrome and mosaic KRAS mutation. *J Craniofac Surg*. 2019;30(1):184-185.
4) Baigrie D, Troxell T, Cook C. Nevus sebaceus. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
5) Tripp JH, Joseph MC, Reay HA. A new neurocutaneous syndrome (skin, eye, brain and heart syndrome). *Proc R Soc Med*. 1971;64(1):23-4.
6) Lovejoy FH Jr, Boyle WE Jr. Linear nevus sebaceus syndrome: report of two cases and a review of the literature. *Pediatrics*. 1973;52(3):382-7.
7) Fahnenstich H, Biltz H, Kreysel HW. Organoid nevus syndrome (Schimmelpenning-Feuerstein-Mims syndrome): case report and literature. *Klin Padiatr*. 1989;201(1):54-7.
8) Van de Warrenburg BP, van Gulik S, Renier WO, et al. The linear naevus sebaceus syndrome. *Clin Neurol Neurosurg*. 1998;100(2):126-32.
9) Krause MH, Ulrich J, Gollnick H. Systematic sebaceous nevus with multiple secondary tumors as the chief symptom of Schimmelpenning-Feuerstein-Mims syndrome. *Hautarzt*. 2001;52(4):339-43.
10) Greene AK, Rogers GF, Mulliken JB. Schimmelpenning syndrome: an association with vascular anomalies. *Cleft Palate Craniofac J*. 2007;44(2):208-15.
11) Lena CP, Kondo RN, Nicolacópulos T. Do you know this syndrome? Schimmelpenning-Feuerstein-Mims syndrome. *An Bras Dermatol*. 2019;94(2):227-9.
12) Pavlidis E, Cantalupo G, Boria S, et. al Hemimegalencephalic variant of epidermal nevus syndrome: case report and literature review. *Eur J Paediatr Neurol*. 2012;16(4):332-42.
13) Miao C, He R, Yang S, Zhang B. Schimmelpenning-Feuerstein-Mims syndrome: a case series and brief literature review of genetically ascertained cases. *J Eur Acad Dermatol Venereol*. 2023;37(3):e438-e440.
14) Kiedrowicz M, Kacalak-Rzepka A, Królicki A, Maleszka R, Bielecka-Grzela S. Therapeutic effects of CO_2 laser therapy of linear nevus sebaceous in the course of the Schimmelpenning-Feuerstein-Mims syndrome. *Postepy Dermatol Alergol*. 2013;30(5):320-3.
15) Resende C, Araújo C, Vieira AP, et al. Schimmelpenning syndrome. *Dermatol Online J*. 2013;19(10):20026.
16) Wang SM, Hsieh Ya-Ju, Chang K-M, et al. Schimmelpenning syndrome: a case report and literature review. *Pediatr Neonatol*. 2014;55(6):487-90.
17) Park PG, Park E, Hyun HS, et al. Cutaneous skeletal hypophosphatemia syndrome in association with a mosaic HRAS mutation. *Ann Clin Lab Sci*. 2018;48(5):665-9.
18) Dwiyana RF, Hazari MN, Diana IA, et al Schimmelpenning syndrome with large nevus sebaceous and multiple epidermal nevi. *Case Rep Dermatol*. 2020;12(3):186-91.
19) Gupta A, Goel S, Thapar RK. Schimmelpenning syndrome: a neuro-oculo-cutaneous disorder. *Indian Dermatol Online J*. 2023;14(6):920-1.
20) Maldar SB, Pinto CJ, Kumar U, Vairaprakasam SP. Schimmelpenning-Feuerstein-Mims syndrome with benign enlargement of subarachnoid space in infancy. *BMJ Case Rep*. 2023;16(11):e257142.
21) Yeager LB, Casper DS, Del Portillo A, Marr BP. Schimmelpenning-Feuerstein-Mims syndrome with orbital choristoma and KRAS mutation: a current review and novel case report. *Ophthalmic Genet*. 2024;45(3):252-7.
22) Ono H, Yamaguchi R, Arai M, et al. Schimmelpenning-Feuerstein-Mims syndrome induced by HRAS Gly12Ser somatic mosaic mutation: case report and literature review. *J Dermatol*. 2023;50(9):1213-5.
23) Menascu S, Donner EJ. Linear nevus sebaceous syndrome: case reports and review of the literature. *Pediatr Neurol*. 2008;38(3):207-10.
24) Happle R. The group of epidermal nevus syndromes Part I. Well defined phenotypes. *J Am Acad Dermatol*. 2010;63(1):1-22.
25) Zutt M, Strutz F, Happle R, et al. Schimmelpenning-Feuerstein-Mims syndrome with hypophosphatemic rickets. *Dermatology*. 2003;207(1):72-6.
26) Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet*. 2019;393(10189):2416-27.
27) Huynh C, Gillis A, Fazendin J, Abdullatif H. A case report to assess the safety and efficacy of Burosumab, an investigational antibody to FGF23, in a single pediatric patient with Epidermal Nevus Syndrome and associated hypophosphatemic rickets. *Bone Rep*. 2022;17:101605.
28) Vera-Duarte GR, Eskenazi-Betech R, De la Fuente Batta I, et al. Unveiling the complexity of Schimmelpenning-Feuerstein-Mims syndrome: a comprehensive case study. *Am J Ophthalmol Case Rep*. 2025;38:102321.
29) Hosalkar HS, Jones DH, Offiah A, Hall C. Linear sebaceous naevus syndrome and resistant rickets. *J Bone Joint Surg Br*. 2003;85(4):578-83.