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Clinically Suspected Mosaic Legius Syndrome in a Yemeni Adolescent: A Rare Case Report

Keywords: Legius Syndrome; Mosaicism; Café-Au-Lait Macules; Neurofibromatosis Type 1; Partial Unilateral Lentiginosis

Abstract

Legius syndrome, also known as neurofibromatosis type 1 (NF1)-like syndrome, is an autosomal dominant condition characterized by café-au-lait macules (CALMs) and freckling in the axilla or other sites, without neurofibromas. Herein, we present a 14-year-old girl with a two-year history of four CALMs on the forehead, left temple, left arm, and right side of the back. Cutaneous examination revealed lentigines on the axilla, chest, and right side of the back. Mosaic NF1 was considered due to unilateral CALMs and axillary freckling; however, neurofibromas were absent. Based solely on typical clinical findings, mosaic Legius syndrome was diagnosed.

Open Access Case Report

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Introduction

Legius syndrome, also known as neurofibromatosis type 1 (NF1)-like syndrome, is an autosomal dominant disorder first described by Brems et al. in 2007 [1] It is characterized by café-au-lait macules (CALMs) and axillary or intertriginous freckling in the absence of the neurofibromas typically observed in NF1 [1] Additional dysmorphic features may include hypertelorism, macrocephaly, lipomas, mild learning difficulties, and attention deficits [2,3]. The disorder is caused by pathogenic variants in the *SPRED1* gene, which encodes Sprouty-related EVH1 domain–containing protein 1 (SPRED1), a negative regulator of the RAS-MAPK signaling pathway involved in cellular growth and development [3]. Herein, we describe a clinically diagnosed case of mosaic Legius syndrome in an adolescent girl.

Case report

A 14-year-old girl presented with a two-year history of multiple CALMs on the forehead, left temple, left arm, and right side of the back (Figures 1–3). Cutaneous examination revealed freckling over the axilla, chest, and right side of the back. No neurofibromas, learning disabilities or developmental delays were identified. Ophthalmologic examination showed no evidence of Lisch nodules, and orthopedic evaluation revealed no osseous abnormalities characteristic of NF.

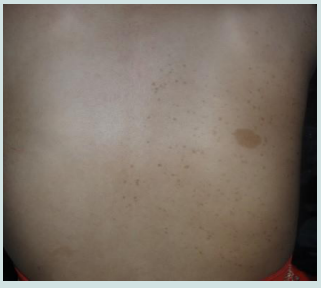

Figure 1: Unilateral café-au-lait macule associated with localized freckling on the right side of the back, demonstrating a mosaic distribution pattern.

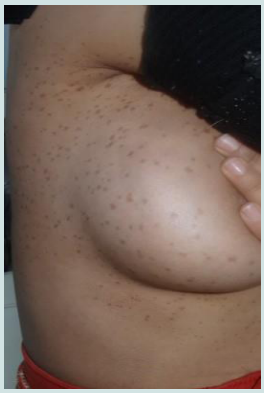

Figure 2: Lentigines involving the right axilla, breast, and abdomen.

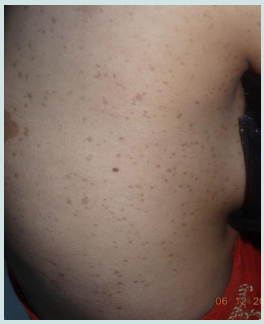

Figure 3: Right lateral view showing the large café-au-lait macule and lentigines covering the right side of the trunk.

Partial unilateral lentiginosis (PUL) was initially considered owing to the segmental distribution of the lesions on the right side of the trunk; however, the presence of four CALMs and ipsilateral axillary freckling complicated the diagnosis. Literature search revealed similar cases of PUL with CALMs and additional axillary freckling, while a few reports described co-occurrence with Lisch nodules. The concomitance of

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Table 1: Additional differential diagnoses.

Condition	Distinguishing Features
Mosaic NF1	Neurofibromas, Lisch nodules, NF1 mutation
Constitutional mismatch repair deficiency	Multiple CALMs, predisposition to malignancies
McCune–Albright syndrome	CALMs with endocrine abnormalities
Segmental pigmentation disorder	Pigmentary lesions without NF1 features
Other RASopathies	Variable systemic manifestations

PUL, axillary freckling, and CALMs in the present case raised the possibility of mosaic neurofibromatosis; however, the absence of neurofibromas rendered this diagnosis less likely and instead favored a diagnosis of Legius syndrome [4-6] Other differential diagnoses are listed in (Table 1). No family members exhibited similar cutaneous findings. Based on the clinical presentation, a diagnosis of mosaic Legius syndrome was made; however, molecular confirmation was not available. Because the patient was only concerned about the cosmetic appearance of the CALMs, treatment was initiated with a Q-switched Nd:YAG laser, followed by topical adapalene gel and kojic acid. Four months after two treatment sessions, patient satisfaction and objective clinical improvement were observed.

This case underscores the diagnostic complexity of mosaic pigmentary disorders, particularly when clinical features overlap with those of mosaic NF1(Table 1).

Discussion

Mosaic Legius syndrome closely resembles mosaic NF1 but is distinguished by the absence of neurofibromas and generally exhibits a milder clinical phenotype [7]. Key clinical features that aid in differentiating Legius syndrome from NF1 are summarized in Table 2. However, recent reports of Lisch nodules in two siblings with Legius syndrome suggest that the phenotypic distinction between Legius syndrome and NF1 may be less absolute than previously recognized [8] Accurate diagnosis is therefore essential for differentiating Legius syndrome from other disorders with similar features, such as NF1, as it can prevent unnecessary malignancy surveillance and alleviate familial anxiety regarding NF1-related complications [9] Nevertheless, reports of SPRED1-associated leukemia suggest that some degree of clinical vigilance may still be warranted [10].

Table 2: Clinical features distinguishing Legius syndrome from NF1.

Feature	Legius Syndrome	NF1
Café-au-lait macules	Common	Common
Axillary freckling	Common	Common
Neurofibromas	Absent	Common
Lisch nodules	Rare	Common
Optic pathway glioma	Not typical	May occur
Gene involved	SPRED1	NF1
Malignancy risk	Lower	Higher

Although genetic testing for *SPRED1* variants could have confirmed our diagnosis, such testing was not available. Nonetheless, this clinically diagnosed case highlights a rare mosaic presentation of Legius syndrome and expands the limited dermatologic literature from resource-constrained settings. Regarding the treatment of PUL and CALMs, available evidence supports the efficacy and safety of Q-switched Nd: YAG laser. Accordingly, this treatment was initiated because the patient was concerned only about the cosmetic burden associated with CALMs.

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