

The Skin as a Diagnostic Anchor: Complete Mucocutaneous Phenotype of Neurofibromatosis Type 1 in A Young Adult with Severe Dystrophic Cervical Kyphosis

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ABSTRACT

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumor-predisposition syndrome caused by pathogenic variants in the NF1 gene and characterized by significant phenotypic variability. Pigmentary and cutaneous lesions, such as café-au-lait macules, skinfold freckling, and dermal or plexiform neurofibromas, occur in nearly all affected individuals and form the core diagnostic criteria. These features often provide the earliest indication of NF1 before neurological, skeletal, or ophthalmological complications. Complete cutaneous phenotypes are less frequently documented when extracutaneous manifestations predominate, and pigmentary-pilar markers of subclinical internal disease are often overlooked.

A 20-year-old man was evaluated after experiencing four years of progressive axial cervical pain following a motorcycle accident, accompanied by radicular pain and gait disturbance that necessitated wheelchair use. Imaging revealed severe destruction of the C5-C6 vertebral bodies with kyphotic deformity, subsequently identified as compressive myelopathy secondary to NF1. Skeletal and surgical findings are reported separately. The patient's father, two paternal aunts, and paternal grandmother exhibited cutaneous lesions consistent with neurofibromas across three generations, supporting autosomal dominant inheritance. Independent of the skeletal assessment, a systematic mucocutaneous examination identified multiple café-au-lait macules on the trunk, axilla, thigh, and leg; bilateral axillary and inguinal freckling extending atypically to the neck and palmoplantar surfaces; and hyperpigmented, hypertrichotic patches on the right arm and left hand. The family reported a dorsal patch with hypertrichosis that could not be examined due to cervical immobilization. The patient fulfilled four of the seven revised 2021 NF1 criteria (≥ 6 café-au-lait macules, axillary/inguinal freckling, ≥ 2 cutaneous neurofibromas, and an affected first-degree relative), exceeding the two required for diagnosis.

Although a multigenerational cutaneous phenotype was present, the diagnosis was established only after four years of orthopedic and neurological symptoms. This case illustrates how systemic complications of NF1 can delay recognition of a diagnosis that could have been identified earlier through a structured skin examination. Freckling extending beyond the classic axillary and inguinal distribution to the neck and palmoplantar surfaces warrants further characterization. Hyperpigmentation and hypertrichosis overlying the skin are recognized markers of underlying plexiform neurofibroma, which often remains occult and carries a lifelong risk of malignant transformation. In this patient, imaging did not confirm these markers, and targeted MRI of the affected limbs is recommended next. The unexamined dorsal lesion and the three-generation pedigree further inform follow-up priorities and genetic counseling.

The complete mucocutaneous phenotype in this patient was sufficient to establish the diagnosis of NF1, despite the initial presentation with a rare and severe skeletal complication. This case

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underscores the importance of systematic skin examination and suggests that pigmentary-pilar markers may indicate clinically silent internal disease.

KEYWORDS: cafe au lait macules, cervical kyphosis, neurofibromatosis 1, spinal cord injury, vertebral destruction syndrome

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I. INTRODUCTION

Neurofibromatosis type 1 (NF1) is a complex autosomal dominant disorder resulting from germline mutations in the NF1 tumor-suppressor gene. This gene encodes neurofibromin, a negative regulator of the RAS/MAPK pathway. NF1 involves multiple organ systems and demonstrates considerable clinical variability, even among members of the same family ^{1,2}.

Pigmentary and cutaneous manifestations, including café-au-lait macules, skinfold freckling, and dermal or plexiform neurofibromas, are observed in nearly all individuals with NF1 and form the basis of the diagnostic criteria. As these lesions are typically visible from early childhood, comprehensive skin examination often yields the earliest and most accessible diagnostic clues, preceding the onset of neurological, skeletal, or ophthalmological complications by several years ³.

In 2021, an international consensus group updated the original 1987 NIH diagnostic criteria, refined the definitions of several mucocutaneous features, and incorporated confirmatory genetic testing as an additional diagnostic approach ^{3,4}. According to both the original and revised frameworks, the presence of two or more defining features, most of which are cutaneous, is sufficient to establish a clinical diagnosis.

Detailed accounts of the complete mucocutaneous phenotype in individual patients are infrequently reported when the primary clinical issue is extracutaneous. Subtle pigmentary and pilar markers, which may indicate clinically silent internal disease, are often overlooked when the focus is on the presenting complaint. This report describes a young man who presented with severe cervical kyphosis and compressive myelopathy, as detailed separately. A systematic dermatological evaluation documented a complete NF1 cutaneous phenotype, along with several additional clinically relevant findings.

II. CASE PRESENTATION

A 20-year-old man presented with a four-year history of progressive axial cervical pain following a motorcycle accident, later accompanied by radicular pain and worsening gait disturbance that ultimately necessitated wheelchair use. Radiographic and tomographic imaging demonstrated severe destruction of the C5-C6 vertebral bodies with kyphotic deformity, attributed to compressive myelopathy secondary to neurofibromatosis type 1 (NF1). Comprehensive skeletal and surgical findings are detailed elsewhere. This clinical

scenario prompted referral for medical genetics assessment and a systematic dermatological evaluation.

Cervical kyphotic deformity is an uncommon but potentially severe skeletal manifestation of NF1; dystrophic curves respond poorly to bracing or posterior fusion alone, and the literature widely reports combined anterior-posterior correction as the most reliable strategy for durable correction ^{5,6}.

The patient's father, two paternal aunts, and paternal grandmother reportedly exhibited multiple cutaneous lesions consistent with neurofibromas, indicating a three-generation pattern suggestive of autosomal dominant inheritance.

A. Mucocutaneous Findings

1) Café-au-lait macules: Multiple lesions were identified, including two on the trunk (approximately 2 x 1.5 cm each) (Figure 1), seven on the lumbar region (Figure 2), one in the right axilla (2 x 4 cm) (Figure 3), and one on the medial leg (3 x 2.5 cm).



Figure 1: Two café-au-lait macules in the dorsal region with surrounding freckling.



Figure 2: seven café-au-lait spots in the lumbar region

2) **Skinfold freckling:** Bilateral axillary and inguinal freckling was present, with additional involvement of the neck, palmar surfaces, and plantar surfaces (Figure 3).



Figure 3: Café-au-lait macule with surrounding freckling on the right axilla

3) **Pigmentary-pilar patches:** Hyperpigmented patches with overlying hypertrichosis were observed on the posterior aspect of the right forearm (Figure 4) and the dorsum of the left wrist (Figure 5).



Figure 4: hyperpigmented, hypertrichotic patch on the anterolateral aspect of the right forearm



Figure 5: hyperpigmented, hypertrichotic patch on the dorsal aspect of the left wrist

4) **Unassessed finding:** The family reported a dorsal patch with hypertrichosis that could not be examined during the evaluation due to cervical immobilization.

5) **Family history:** The patient's father, a first-degree relative, exhibited cutaneous lesions suggestive of NF1.

B. Imaging

1) **X-rays:** Plain radiographs of the cervical spine were obtained, revealing cervical hyperkyphosis and loss of the normal morphology of the C4, C5, and C6 vertebral bodies (Figure 6).



Figure 6: Plain lateral cervical radiograph that demonstrates cervical hyperkyphosis and loss of the normal morphology of the C4, C5, and C6 vertebral bodies.

2) **MRI:** Unenhanced MRI showing a narrow cervical canal with evidence of spinal cord compression at the C2-C3 level and diffuse intramedullary hyperintensities (Figure 7).

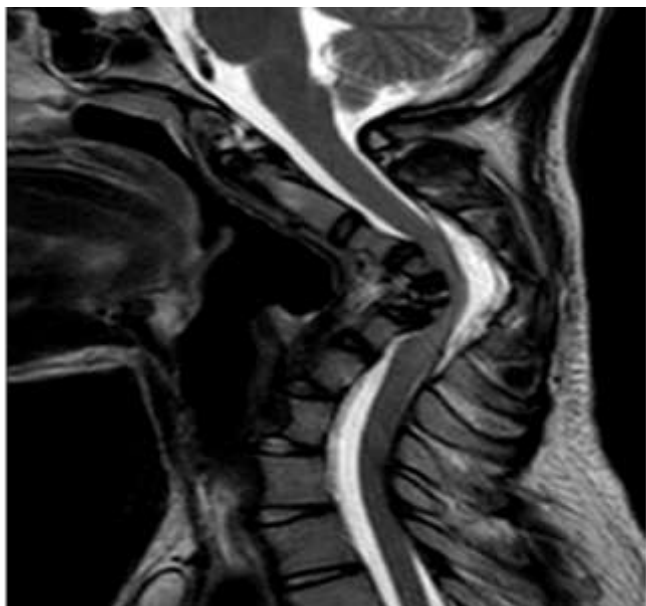


Figure 7: Sagittal section of simple cervical MRI in T2 sequence showing a narrow cervical canal with evidence of spinal cord compression at the C2-C3 level and diffuse intramedullary hyperintensity.

Collectively, the patient met four of the seven revised NIH/2021 diagnostic criteria for NF1: six or more café-au-lait macules, axillary or inguinal freckling, two or more cutaneous neurofibromas, and an affected first-degree relative. This exceeds the two criteria required for a clinical diagnosis. Lisch nodules, optic pathway glioma, and distinctive osseous dysplasia (sphenoid wing dysplasia or long-bone cortical thinning) were not systematically assessed in the available records; these features carry independent clinical relevance — optic pathway gliomas, for instance, occur in a meaningful proportion of children with NF1 and can threaten vision if untreated² — and their absence from this evaluation represents an area for future assessment. The Department of Genetics confirmed the diagnosis following a formal consultation request.

III. DISCUSSION

Despite an extensive, longstanding, and multigenerational cutaneous phenotype, the diagnosis of NF1 in this patient was established only after four years of progressive orthopaedic and neurological symptoms. Although multiple relatives across three generations had cutaneous findings consistent with NF1, this pattern had apparently not been recognized by the family as a hereditary syndrome prior to this evaluation. This scenario resembles the diagnostic delay described in patients without a recognized family history of NF1, in whom cutaneous findings are frequently overlooked or attributed to unrelated causes⁷. This sequence shows that systemic complications of NF1 are able to overshadow cutaneous manifestations and delay recognition of a diagnosis that a structured mucocutaneous examination might have established earlier. This data support incorporating a

systematic skin survey early in the evaluation of unexplained skeletal or neurological disease in young patients, particularly when a compatible family history is present.

The extension of skinfold freckling to the neck, palmar, and plantar surfaces, beyond the classic axillary and inguinal (Crowe sign) distribution, is a descriptive finding in this patient¹.

Hyperpigmentation or hypertrophy of the overlying skin, together with patches of coarse hair, is a recognized clinical sign of an underlying plexiform neurofibroma. This diffuse, unencapsulated tumor can involve multiple nerve branches and may be visible on the skin in some patients while remaining undetectable on physical examination in others. Up to half of plexiform lesions are identified only through whole-body imaging⁸. Plexiform neurofibromas are a leading cause of morbidity in NF1, stressing the clinical importance of their identification^{1,8}. Their lifetime risk of conversion into a malignant peripheral nerve sheath tumor has been estimated at 8-13%⁹. In this patient, the hyperpigmented, hypertrichotic patches on the right arm and left hand raise clinical suspicion for an underlying plexiform component; however, no confirmatory imaging of the extremities was obtained, and this association is still a clinical impression rather than a confirmed finding. Targeted magnetic resonance imaging of the affected limbs would be a reasonable next step to clarify the diagnosis and establish a baseline for long-term surveillance.

The dorsal patch with hypertrichosis reported by the family, but not assessable at the time of evaluation due to cervical immobilization, remains unresolved. A follow-up dermatological examination and photographic documentation after discontinuation of immobilization would complete the mucocutaneous survey and determine if this lesion has similar significance to the extremity findings described above.

The three-generation, autosomal dominant pedigree observed in this family further accentuates the importance of dermatological recognition in prompting genetic counseling and cascade screening of at-risk relatives, independent of the skeletal phenotype that led to this patient's surgical evaluation¹⁰.

This report has several restrictions inherent to a single-patient design. The diagnosis of the cutaneous neurofibromas was clinical, without dermoscopic or histopathological confirmation. Imaging did not confirm the extremity pigmentary-pilar patches, and the dorsal lesion could not be examined. These gaps are presented transparently as directions for continued multidisciplinary follow-up rather than as established findings.

IV. CONCLUSIONS

This patient presented a complete mucocutaneous phenotype of NF1 that, independently, was sufficient to establish the diagnosis on clinical grounds, in a case whose

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presenting complaint was a rare and severe skeletal complication. The findings reinforce the diagnostic value of a systematic, comprehensive skin examination in NF1 and suggest that specific pigmentary-pilar markers may indicate clinically silent internal disease warranting targeted imaging. The unexamined and radiologically unconfirmed findings identified in this report define concrete next steps for this patient's multidisciplinary follow-up.

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