ACCSCIENCE PUBLISHING

Tumor Discovery

CASE REPORT

When the signs are missed: A pediatric case of late-diagnosed neurofibromatosis type I with complex comorbidities

Sabah Sikandar[1], Christopher Alexander[2], Maheen Qayyum[3], Sydney Molenaar[1], Hiba Ahmad[1], Anoshia Ali[4], Isra Mustansar[4], David Johnson[5], Zafar Qureshi[6]*, and Syed A. A. Rizvi[7]*

[1]Dr. Kiran C Patel College of Osteopathic Medicine, Nova Southeastern University, Fort Lauderdale, Florida, United States of America

[2]Ross University School of Medicine, Miramar, Florida, United States of America

[3]Barry University, Miami, Florida, United States of America

[4]Dow Medical College, Karachi, Pakistan

[5]William Carey University College of Osteopathic Medicine, Hattiesburg, Mississippi, United States of America

[6]UMC Free Clinic, Miami Gardens, Florida, United States of America

[7]College of Biomedical Sciences, Larkin University, Miami, Florida, United States of America

***Corresponding authors:**
Syed A. A. Rizvi
(srizvi@larkin.edu)
Zafar Qureshi
(drqureshimd@gmail.com)

Citation: Sikandar S, Alexander C, Qayyum M, *et al*. When the signs are missed: A pediatric case of late-diagnosed neurofibromatosis type I with complex comorbidities. *Tumor Discov*. 2025;4(4):163-170. doi: 10.36922/TD025320077

Received: August 6, 2025

Revised: August 26, 2025

Accepted: September 2, 2025

Published online: September 18, 2025

Abstract

Neurofibromatosis type I (NF1) is an autosomal dominant neurocutaneous disorder characterized by a mutation in the *NF1* gene, leading to loss of neurofibromin function and subsequent hyperactivation of the Ras-MAPK signaling pathway. Early diagnosis is critical to initiate appropriate surveillance and therapeutic interventions, yet clinical recognition can be challenging due to phenotypic variability and frequent *de novo* mutations. This case highlights a 17-year-old male with a delayed NF1 diagnosis due to initially inconclusive clinical features and limited family history. The diagnosis was confirmed only after the development of multiple hallmark findings, including café-au-lait macules, axillary freckling, Lisch nodules, and a symptomatic plexiform neurofibroma. The delay in diagnosis resulted in missed opportunities for early intervention and surveillance. The patient was eventually started on selumetinib, a mitogen-activated protein kinase inhibitor approved for inoperable plexiform neurofibromas. This case underscores the importance of early clinical suspicion, timely genetic confirmation, and multidisciplinary management to improve outcomes in NF1.

Keywords: Neurofibromatosis type I; Von Recklinghausen's disease; Plexiform neurofibroma; Café au lait macules; Lisch nodules; Neurocutaneous syndrome

1. Background

Neurofibromatosis type I (NF1) is an autosomal dominant neurocutaneous genetic disorder that affects approximately 1 in 2,500 to 1 in 3,000 live births.[1] It results from a loss-of-function mutation in the *NF1* tumor suppressor gene located on chromosome

17q11.2, which encodes neurofibromin, a protein that negatively regulates the Ras signaling pathway.[1] Notably, about 42% of NF1 cases arise from *de novo* mutations, obviating the need to diagnose based on a positive family history.[2]

Neurofibromin acts as a GTPase-activating protein, accelerating the inactivation of Ras, a proto-oncogene integral to cell growth and differentiation. This protein is widely expressed, with particularly high concentrations in the nervous system.[3] Mutations in *NF1* disrupt this regulatory function, leading to unrestrained Ras activity, cellular proliferation, and tumor development across various organ systems. Clinically, this manifests as multiple neurofibromas (benign peripheral nerve sheath tumors), pigmentary abnormalities such as café-au-lait macules, and an increased risk of central nervous system (CNS) gliomas.[4]

The clinical presentation of NF1 is highly variable. Café-au-lait macules are typically the earliest and most consistent sign, present in approximately 99% of affected individuals by age one.[3] Additional features include axillary and inguinal freckling; Lisch nodules (benign iris hamartomas); and neurofibromas, which are Schwann-cell tumors composed of a variety of neoplastic and non-neoplastic cells. Plexiform neurofibromas—benign, deeply infiltrative tumors involving multiple nerve fascicles—are also characteristic. Skeletal abnormalities, including osteopenia, scoliosis, sphenoid wing dysplasia, congenital tibial bowing, and pseudoarthrosis, are common manifestations. Cardiovascular anomalies such as congenital heart disease, vasculopathy, and hypertension may also occur, along with neurocognitive deficits.[3,5]

NF1 significantly increases the lifetime risk for various malignancies, including optic pathway gliomas, glioblastomas, malignant peripheral nerve sheath tumors, gastrointestinal stromal tumors, pheochromocytomas, leukemias, and breast cancers, particularly in individuals with existing internal plexiform neurofibromas. Given the progressive and lifelong nature of NF1, comprehensive care strategies incorporating multidisciplinary management, early detection, and targeted interventions are essential to optimizing patient outcomes.[6,7]

Recent work on NF1-associated tumors highlights advances in molecular characterization, therapeutic strategies, and tumor biology. One study identified DLK1 as a marker that helps distinguish molecularly distinct subsets of NF1-associated malignant peripheral nerve sheath tumors, offering potential for more tailored prognostication and treatment approaches.[8] Another review emphasized current management of malignant peripheral nerve sheath tumors, stressing the need for early detection and coordinated multidisciplinary care.[9] Updates on therapeutic strategies underscore the limited efficacy of first-generation RAF inhibitors and the emerging promise of pan-RAF inhibitors such as tovorafenib in pediatric low-grade glioma.[10] Pilocytic astrocytoma has been presented as a prototypical WHO grade I glioma, notable for its favorable prognosis and strong association with MAPK pathway alterations.[11] In addition, investigations into transglutaminase 2 have revealed novel insights into tumor cell biology that could inform future targeted therapies across NF1-related neoplasms.[12] Diagnosis of NF1 is primarily clinical, based on the revised National Institutes of Health (NIH) criteria, with genetic testing reserved for atypical cases or prenatal counseling.[13,14]

A diagnosis is confirmed in individuals without a known affected parent if two or more of the following are present:

(i) Six or more café-au-lait macules (>5 mm in prepubertal individuals or >15 mm in postpubertal individuals)
(ii) Axillary or inguinal freckling
(iii) Two or more neurofibromas of any type or one plexiform neurofibroma
(iv) Optic pathway glioma
(v) Two or more Lisch nodules or choroidal abnormalities
(vi) A characteristic osseous lesion (*e.g.*, sphenoid dysplasia, long bone pseudoarthrosis, tibial bowing)
(vii) A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in non-tumor tissue

In individuals with a parent meeting these diagnostic criteria, the presence of at least one of the above findings is sufficient for diagnosis.

2. Case presentation

The patient is a 17-year-old male with a long-standing history consistent with NF1. The patient was first evaluated at birth in 2008 due to the presence of a few café-au-lait macules and diffuse brown freckling. He was referred to the genetics department; however, at that time, he did not initially meet diagnostic criteria, and formal genetic testing was declined due to financial constraints.

By 2015, several clinical signs showed notable progression, including an increased number of café-au-lait macules, axillary freckling, and bilateral Lisch nodules, all of which fulfilled the NIH criteria for NF1.Therefore, the patient's diagnosis of neurofibromatosis was confirmed in 2015. He also had bilateral myopia, refractive amblyopia (left eye), and exotropia. Magnetic resonance imaging (MRI) of the brain and cervical spine was unremarkable, and echocardiography was recommended for a benign cardiac murmur. In 2018, the patient developed localized pain in the left thigh/groin. MRI revealed a plexiform neurofibroma, which was deemed inoperable due to its

anatomical complexity. He was referred to hematology/oncology department for surveillance. Due to financial constraints, treatment could not be initiated until 2022. However, despite treatment initiation with selumetinib in 2022, lesion progression continued due to nonadherence and persistent financial barriers. In 2019, the patient presented with new-onset tinnitus, which prompted repeat brain imaging that showed hyperintense foci in the posterior fossa (left cerebral peduncle, periaqueductal gray, pons, and bilateral cerebellar white matter), radiographically consistent with NF1.

Ophthalmology surveillance visits increased in frequency from annually to quarterly due to visual abnormalities. His visual acuity improved from 20/40 (2019) to 20/30 (2023). He still exhibited intermittent exotropia and refractive amblyopia in the left eye without optic nerve involvement. The headaches were determined to be non-ocular in origin.

In 2023, cardiac monitoring revealed physiologic tricuspid regurgitation, with a subsequent reduction in left ventricular shortening fraction from 65.4% to 55.5% in 2024. Despite a family history of hypertension and heart disease, the patient's vital signs have remained stable, with blood pressure surveillance ongoing due to the NF1-associated risk of renovascular hypertension.

With regard to neurology surveillance, follow-up MRIs in 2023 and 2025 showed no disease progression.

In 2024, the patient developed chronic dyspepsia lasting nine months, characterized by postprandial nausea and frequent belching. A gastric emptying study was normal; however, the recommended upper endoscopy remains pending. This case highlights a classic but delayed presentation of NF1, marked by progressive cutaneous, ocular, neurological, cardiovascular, and gastrointestinal involvement. It underscores the critical need for early clinical recognition, access to genetic confirmation, and multidisciplinary surveillance to optimize outcomes and minimize NF1-related morbidity.

On presentation, the patient was alert and oriented to person, place, and time. He appeared well-groomed and in no acute distress, with clear speech and age-appropriate behavior. Vital signs were stable, with a sitting blood pressure of 125/69 mmHg and a body mass index of 21 kg/m^2. Physical examination revealed hallmark cutaneous features of NF1, including numerous café-au-lait macules and axillary freckling (Figure 1). A plexiform neurofibroma was noted along the medial aspect of the left proximal thigh (Figure 2), measuring approximately 5–6 cm in width in 2015 and progressively enlarging to 8.0 × 5.5 cm by 2025. The lesion was mildly tender to palpation. The patient rated his pain as 8 out of 10 in severity, with intermittent episodes of radiating discomfort down the leg. Pain intensity was reported to fluctuate, improving to 6/10 or as low as 2/10 with over-the-counter analgesics. Gait and genitourinary function remained intact. He denied nocturnal pain or sleep disturbances attributable to the mass. Although physical therapy was recommended in early 2024 for both mass-related and concurrent back pain, the patient has yet to initiate treatment.

Ophthalmologic evaluation revealed bilateral Lisch nodules and myopia, for which the patient wears corrective lenses. Additional findings included left eye refractive amblyopia and intermittent exotropia. The remainder of the physical examination was within normal limits, with no additional abnormalities detected.

The brain MRI performed in 2019 demonstrated multiple areas of T2-weighted and FLAIR hyperintensity, consistent with regions of myelin vacuolization often seen in pediatric patients with NF1 (Figure 3A). Follow-up MRI in 2022 showed interval improvement of these signal abnormalities, with no new lesions identified (Figure 3B), suggesting radiographic stability or partial resolution (Table 1). While typically benign, NF1 carries an approximate 2% lifetime risk of developing low-grade gliomas of the brain.

Initial MRI of the left femur and thigh in 2015 revealed a large plexiform neurofibroma measuring approximately 20 cm craniocaudally. Serial imaging in early and late 2022 (Figures 4 and 5A) demonstrated progressive enlargement to 24.8 × 5.4 × 3.8 cm and then 26.7 × 5.7 × 3.9 cm, respectively. An MRI obtained in early 2025 showed further growth, with the lesion expanding to 29 × 7 × 5.8 cm, infiltrating adjacent muscle groups and fascial planes. A repeat MRI in late 2025 (Figure 5B) indicated no additional size progression, suggesting temporary stabilization (Table 2).

Cardiac evaluation through echocardiography in 2023 revealed physiologic tricuspid regurgitation with no structural abnormalities. However, follow-up imaging in 2024 demonstrated a reduction in the left ventricular shortening fraction to 55.5%, approximately a 10% decrease from 65.4% recorded from the previous year.

Renal ultrasound findings were normal, showing no evidence of hydronephrosis or renal artery stenosis, conditions associated with NF1-related vasculopathy. Routine laboratory assessments revealed transient neutropenia and albuminuria in 2022 and 2023, both of which resolved by 2024, indicating no ongoing hematologic or renal compromise.

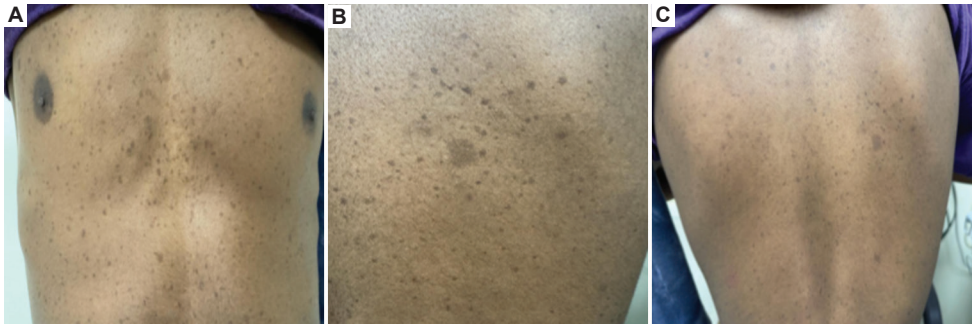

Figure 1. Diffuse café-au-lait macules and freckling present on the patient in July 2025: (A) on the anterior chest and abdomen; (B) on the back (narrowed view); (C) on the back (overview)

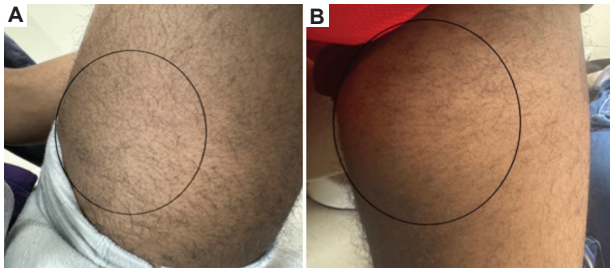

Figure 2. Size progression of the plexiform neurofibroma on the left proximal thigh from 5 to 6 cm in width in 2015 (A) to 8 × 5.5 cm in July 2025 (B)

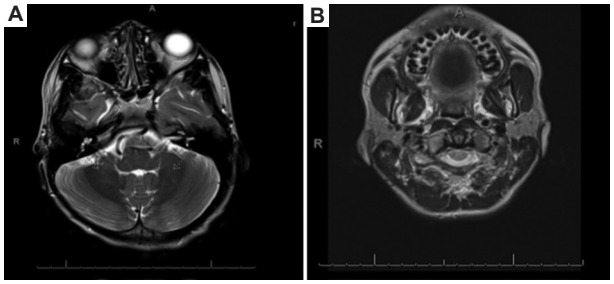

Figure 3. Sequential brain magnetic resonance imaging (MRI) in a child with Neurofibromatosis Type I. (A) Brain MRI in August 2019 demonstrates multiple sites of hyperintense T2 and FLAIR signal, characteristic of myelin vacuolization in this condition. (B) Brain MRI in September 2022 shows interval improvement of these abnormalities, with resolution of previously noted lesions and no evidence of new hyperintense signals.

The patient had consistently reported experiencing significant pain and emotional distress related to his condition. He characterized his diagnosis as burdensome, largely due to the need for ongoing imaging, frequent medical evaluations, and the associated disruption to his daily life. These medical demands, coupled with chronic discomfort, have adversely affected his ability to engage in physical activities such as sports and extended walking. In addition, the patient carries coexisting diagnoses of developmental delay and autism spectrum disorder, both of which have a higher prevalence among individuals with NF1. Consequently, he requires assistance with activities of daily living and ongoing supervision to ensure his safety, particularly in preventing elopement and self-injurious behaviors.

Table 1. Brain lesion progression based on MRI findings

Visit	Year	Imaging findings
Initial	2019	Multiple areas of T2-weighted and FLAIR hyperintensity, consistent with regions of myelin vacuolization (Figure 3A).
Follow-up	2022	MRI showed interval improvement of previously noted areas of myelin vacuolization. No new signal hyperintensity was seen (Figure 3B).
Follow-up	2023	MRI showed no disease progression.
Follow-up	2025	MRI showed no disease progression.

Abbreviation: MRI: Magnetic resonance imaging.

Table 2. Left thigh neurofibroma progression based on MRI findings

Visit	Year	Imaging findings
Initial	2022	Sagittal view of the thigh-cross section of a multi-spatial soft tissue mass measuring 24.8×5.4×3.8 cm.
Follow-up	2022	MRI showed an increase in size of the soft tissue mass measuring 26.7×5.7×3.9 cm.
Follow-up	2025	MRI showed a further increase in size of the soft-tissue mass measuring 29×7 × 5.8 cm.

Abbreviation: MRI: Magnetic resonance imaging.

A comprehensive differential diagnosis was considered based on the patient's clinical presentation. The primary conditions evaluated included Legius syndrome, constitutional mismatch repair deficiency syndrome (CMMR-D), and neurofibromatosis type II (NF2)-related schwannomatosis.[15]

Legius syndrome shares several overlapping phenotypic features with NF1, including multiple café-au-lait macules, axillary freckling, and macrocephaly.[16] However, it lacks

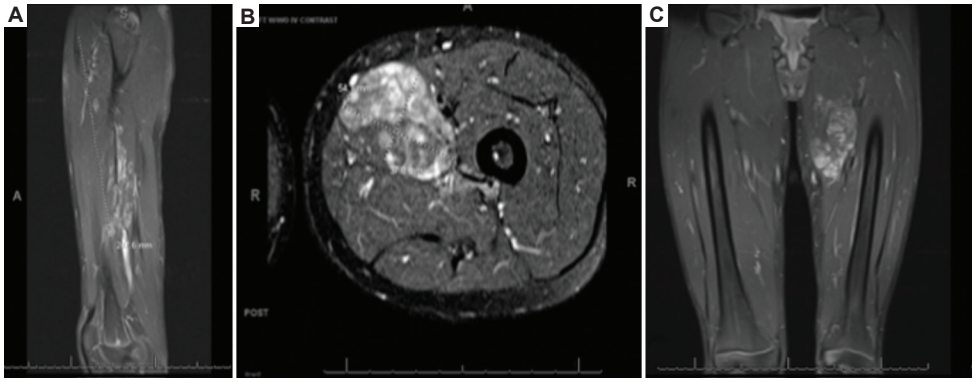

Figure 4. Magnetic resonance imaging of left thigh in February 2022. (A) Sagittal view of the thigh; (B) Cross section of a multi-spatial soft tissue mass measuring 24.8 × 5.4 × 3.8 cm; (C) Frontal view of soft tissue mass.

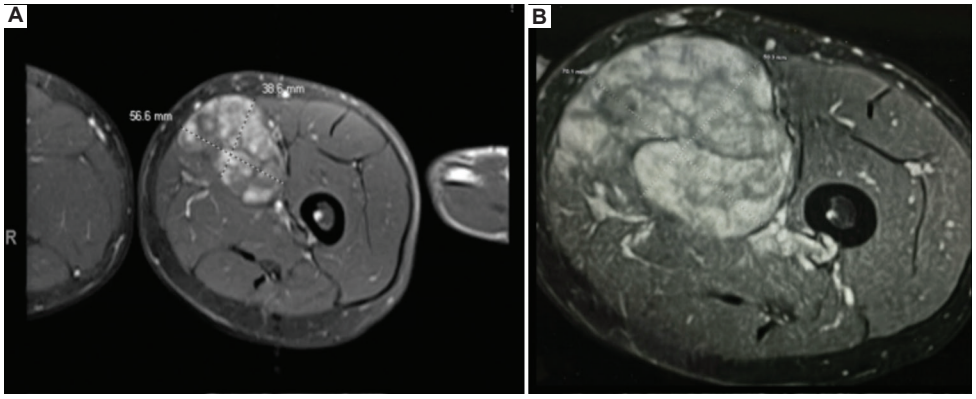

Figure 5. Serial magnetic resonance imaging (MRI) of the left thigh demonstrating progressive enlargement of a soft tissue mass. (A) MRI in September 2022 shows a mass measuring 26.7 × 5.7 × 3.9 cm. (B) Cross-sectional MRI on June 26, 2025, reveals further increase in size, with dimensions of 29 × 7 × 5.8 cm.

hallmark findings of NF1, such as neurofibromas and CNS tumors, both of which were present in this patient. The presence of a plexiform neurofibroma and Lisch nodules strongly favors a diagnosis of NF1 over Legius syndrome. CMMR-D syndrome is a rare autosomal recessive disorder caused by mutations in DNA mismatch repair genes and is associated with a heightened risk for childhood malignancies. While café-au-lait macules may be observed in both CMMR-D and NF1, the constellation of findings in this patient. Including Lisch nodules, a plexiform neurofibroma, and progressive clinical features consistent with NF1, support NF1 as the more likely diagnosis.[17,18]

NF2-related schwannomatosis was also considered, particularly considering the patient's symptoms of headaches and tinnitus. NF2 typically presents with bilateral vestibular schwannomas and may include intracranial and spinal meningiomas. However, Lisch nodules are not characteristic of NF2, and café-au-lait macules are uncommon, making NF1 the more appropriate diagnosis in this case.[19] Ultimately, the most definitive method for distinguishing NF1 from these phenotypically similar conditions is molecular genetic testing, which can confirm the presence of a pathogenic *NF1* mutation and rule out alternative diagnoses. However, in the case of this patient, due to financial constraints, genetic testing was not pursued.

The patient's plexiform neurofibroma was deemed inoperable by orthopedic surgery due to its anatomical location and the high risk of morbidity and potential mortality associated with resection. Consequently, the patient was initiated on medical therapy with selumetinib, a mitogen-activated protein kinase (MEK) inhibitor, at a dosage of 25 mg twice daily. Selumetinib has demonstrated efficacy in reducing the volume of inoperable plexiform neurofibromas and alleviating associated symptoms in patients with NF1. Recently, newly FDA-approved drugs cabozantinib and mirdametinib have also proven their efficacy in the adult population. Other MEK inhibitors such as trametinib and binimetinib have also demonstrated promising preliminary results.[20,21]

In parallel with pharmacologic management, the patient underwent periodic MRI surveillance to assess

progression of the plexiform neurofibroma and screen for the emergence of optic pathway gliomas. Ophthalmologic evaluations were initially conducted annually but have since increased in frequency to every 6 months and now every three months, focusing on visual acuity and the status of ocular manifestations, including Lisch nodules and amblyopia.

This multidisciplinary surveillance strategy encompassing oncology, orthopedics, ophthalmology, and radiology highlights the critical importance of integrated, coordinated care in the management of NF1. Such an approach facilitates timely identification and intervention for disease-related complications, ultimately improving patient outcomes.

Recent immunologic assessment (July 2025) revealed a positive antinuclear antibody screen via indirect immunofluorescence assay with a titer of 1:40 (interpreted as negative) and a nuclear staining pattern. Given these findings, the patient was referred to a rheumatologist for further evaluation. Although the coexistence of autoimmune disorders in individuals with NF1 appears to be rare, several case reports suggest potential associations. Notably, pediatric NF1 cases have coincided with anti-muscle-specific kinase antibody–positive myasthenia gravis and juvenile idiopathic arthritis.[22] In isolated adult cases, NF1 has been reported alongside vitiligo, alopecia areata, and autoimmune thyroiditis.[23] Furthermore, five or more reported cases of co-occurring NF1 and systemic lupus erythematosus have been described in the literature, involving both pediatric and adult patients.[24] An additional case report highlights associations between NF1 and other autoimmune conditions such as Hashimoto's thyroiditis, diabetes mellitus, multiple sclerosis, and vitiligo.[25] While these observations raise the possibility of pathogenic links potentially via neurofibromin-related immune dysregulation, such associations remain unproven. Larger epidemiologic studies are necessary to establish causality or confirm coincidence.

3. Discussion

The patient described in this case was initially evaluated for limited café-au-lait macules at birth but did not meet the NIH diagnostic criteria for NF1 at that time and lacked a contributory family history. By age seven, he developed additional clinical features consistent with NF1, including more than six café-au-lait macules larger than 5 mm, bilateral Lisch nodules, and a plexiform neurofibroma, thus fulfilling diagnostic criteria for NF1. As the disease progressed, he experienced intermittent headaches and tinnitus, which prompted neuroimaging. MRI of the brain revealed hyperintense foci, findings commonly associated with NF1-related myelin vacuolization and helped to exclude a diagnosis of NF2, which is characterized by bilateral vestibular schwannomas.[26,27]

The patient's plexiform neurofibroma demonstrated progressive enlargement over time. Due to its size and anatomical location in the left proximal thigh, surgical resection was not feasible owing to the associated high morbidity risk. Consequently, he was offered medical therapy with selumetinib, an oral MEK1/2 inhibitor that selectively targets the Ras-Raf-MEK-ERK signaling cascade, which is aberrantly activated in NF1-related tumors. Selumetinib received U.S. FDA approval in 2020 for the treatment of symptomatic, inoperable plexiform neurofibromas in children aged ≥2 years. In the SPRINT phase II trial, 70% of patients achieved a confirmed partial response, defined as ≥20% reduction in tumor volume, with concurrent improvements in pain and physical function.[28]

Despite the potential therapeutic benefit, adherence to selumetinib therapy in adolescents may be hindered by side effects (*e.g.*, gastrointestinal disturbances), limited understanding of its long-term value, lack of supervision, or financial burden. These challenges can significantly compromise treatment efficacy and underscore the need for targeted counseling, adherence support, and coordinated care strategies in pediatric MEK inhibitor therapy.[28,29]

Despite routine counseling, this patient was nonadherent to selumetinib for more than 6 months. According to his mother, noncompliance was multifactorial driven by financial hardship due to the patient's insurance, a lack of consistent medication supervision, and the patient's indifference to continued treatment. She reported that he frequently forgot doses and expressed diminishing motivation over time. The lack of insurance coverage played a major role in nonadherence and lack of genetic testing.

This case highlights that even subtle early signs such as café-au-lait macules and diffuse freckling should prompt proactive surveillance for NF1, even before full NIH criteria are met. As the earliest indicators of NF1, these pigmentary features warrant structured follow-up and, when possible, genetic testing. Reliance solely on diagnostic thresholds risks delayed recognition, missed opportunities for intervention, and greater morbidity. Clinicians must remain vigilant and initiate monitoring when characteristic but incomplete features are present. Equally important, successful management of NF1 requires strong family engagement, socioeconomic support, adequate insurance coverage, and tailored adherence strategies to ensure long-term continuity of care in chronic pediatric conditions.

4. Conclusion

This complex case underscores the necessity of a coordinated, multidisciplinary approach to effectively manage the diverse clinical manifestations of NF1. Geneticists provide diagnostic accuracy and familial counseling; ophthalmologists monitor for optic pathway gliomas and Lisch nodules; radiologists perform serial imaging to assess tumor progression or malignant transformation; orthopedists manage skeletal deformities and assess surgical needs; and oncologists oversee systemic therapies such as selumetinib. Robust follow-up protocols, including annual MRI, regular ophthalmologic evaluations, blood pressure monitoring, and systematic symptom tracking, are essential to minimize long-term complications and optimize clinical outcomes. Given the lifelong risk of malignant transformation and multisystem involvement in NF1, it is imperative that patients engage in ongoing care with subspecialists and adhere to routine surveillance to enable early detection and timely intervention.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Zafar Qureshi, Syed A. A. Rizvi
Formal analysis: All authors
Investigation: All authors
Methodology: All authors
Writing–original draft: All authors
Writing–review & editing: All authors

Ethics approval and consent to participate

This study is not a clinical trial or does not involve multiple patients; therefore, approval from the IRB or ethics committee is not required. The patient provided verbal consent to participate in this study and allowed us to use his scans and medical information without disclosing his identity.

Consent for publication

Verbal consent has been obtained from the patient to publish his data.

Availability of data

Not applicable.

References

1. García B, Catasus N, Ros A, *et al*. Neurofibromatosis type 1 families with first-degree relatives harbouring distinct NF1 pathogenic variants. Genetic counselling and familial diagnosis: What should be offered? *J Med Genet*. 2022;59(10):1017-1023.

   doi: 10.1136/jmedgenet-2021-108301

2. Evans DG, Howard E, Giblin C, *et al*. Birth incidence and prevalence of tumor-prone syndromes: Estimates from a UK family genetic register service. *Am J Med Genet A*. 2010;152A(2):327-332.

   doi: 10.1002/ajmg.a.33139

3. Ly KI, Blakeley JO. The diagnosis and management of neurofibromatosis type 1. *Med Clin North Am*. 2019;103(6):1035-1054.

   doi: 10.1016/j.mcna.2019.07.004

4. Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis. A clinical and population study in South-East Wales. *Brain*. 1988;111(Pt 6):1355-1381.

   doi: 10.1093/brain/111.6.1355

5. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: A multidisciplinary approach to care. *Lancet Neurol*. 2014;13(8):834-843.

   doi: 10.1016/S1474-4422(14)70063-8

6. Chong S. Lifelong management of neurofibromatosis 1 patients. *J Korean Neurosurg Soc*. 2025;68(3):261-271.

   doi: 10.3340/jkns.2025.0057

7. Wang W, Wei CJ, Cui XW, *et al*. Impacts of *NF1* gene mutations and genetic modifiers in neurofibromatosis type 1. *Front Neurol*. 2021;12:704639.

   doi: 10.3389/fneur.2021.704639

8. Mitchell DK, Brewster K, Makri SC, *et al*. DLK1 distinguishes subsets of NF1-associated malignant peripheral nerve sheath tumors with divergent molecular signatures. *Clin Cancer Res*. 2025;31(10):1988-2009.

   doi: 10.1158/1078-0432.CCR-24-3029

9. Hirbe AC, Dehner CA, Dombi E, *et al*. Contemporary approach to neurofibromatosis type 1-associated malignant peripheral nerve sheath tumors. *Am Soc Clin Oncol Educ Book*. 2024;44(3):e432242.

   doi: 10.1200/edbk_432242

10. Na B, Shah SR, Vasudevan HN. Correction to: Past, present, and future therapeutic strategies for NF-1-associated tumors. *Curr Oncol Rep*. 2024;26:1223.

doi: 10.1007/s11912-024-01581-y

11. Pizzimenti C, Fiorentino V, Germanò A, Martini M, Ieni A, Tuccari G. Pilocytic astrocytoma: The paradigmatic entity in low-grade gliomas (review). *Oncol Lett*. 2024;27(4):146.

    doi: 10.3892/ol.2024.14279

12. Buccarelli M, Castellani G, Fiorentino V, *et al*. Biological implications and functional significance of transglutaminase type 2 in nervous system tumors. *Cells*. 2024;13(8):667.

    doi: 10.3390/cells13080667

13. Ferner RE, Gutmann DH. Neurofibromatosis type 1 (NF1): Diagnosis and management. *Handb Clin Neurol*. 2013;115:939-955.

    doi: 10.1016/B978-0-444-52902-2.00053-9

14. Angelova-Toshkina D, Holzapfel J, Huber S, *et al*. Neurofibromatosis type 1: A comparison of the 1997 NIH and the 2021 revised diagnostic criteria in 75 children and adolescents. *Genet Med*. 2022;24(9):1978-1985.

    doi: 10.1016/j.gim.2022.05.013

15. Suerink M, Ripperger T, Messiaen L, *et al*. Constitutional mismatch repair deficiency as a differential diagnosis of neurofibromatosis type 1: Consensus guidelines for testing a child without malignancy. *J Med Genet*. 2019;56(2):53-62.

    doi: 10.1136/jmedgenet-2018-105664

16. Legius E, Messiaen L, Wolkenstein P, *et al*. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: An international consensus recommendation. *Genet Med*. 2021;23(8):1506-1513.

    doi: 10.1038/s41436-021-01170-5

17. Abdelmaksoud-Dammak R, Ammous-Boukhris N, BenAyed-Guerfali D, *et al*. Strategies for diagnosis and management of CMMRD in low-resource countries: Report of a Tunisian family. *Fam Cancer*. 2024;23(4):515-522.

    doi: 10.1007/s10689-024-00386-z

18. Bin Naeem S, Ullah N, Jhatial MA, *et al*. Constitutional mismatch repair deficiency (CMMRD) syndrome: A case report of a patient with multiple metachronous malignancies. *Cureus*. 2023;15(7):e41870.

    doi: 10.7759/cureus.41870

19. Yohay K. Neurofibromatosis types 1 and 2. *Neurologist*. 2006;12(2):86-93.

    doi: 10.1097/01.nrl.0000195830.22432.a5

20. Solares I, Viñal D, Morales-Conejo M, Rodriguez-Salas N, Feliu J. Novel molecular targeted therapies for patients with neurofibromatosis type 1 with inoperable plexiform neurofibromas: A comprehensive review. *ESMO Open*. 2021;6(4):100223.

    doi: 10.1016/j.esmoop.2021.100223

21. Yu Y, Wei C, Yue M, Zhang C, Wang Y, Wang Z. From benign neurofibromas to malignant peripheral nerve sheath tumors (MPNST): A gaming among multiple factors. *Cell Oncol (Dordr)*. 2025;48(4):841-857.

    doi: 10.1007/s13402-025-01054-9

22. Esra S, Ceren G, Erdal S, Hatice B, Fatma E, Banu A. Is there a tendency for autoimmunity in neurofibromatosis type 1? Case reports. *Indian J Pediatr*. 2022;89(5):510-512.

    doi: 10.1007/s12098-021-04010-1

23. Nanda A. Autoimmune diseases associated with neurofibromatosis type 1. *Pediatr Dermatol*. 2008;25(3): 392-393.

    doi: 10.1111/j.1525-1470.2008.00692.x

24. Akyüz SG, Çaltik A, Bülbül M, Erdoğan Ö, Renda R, Demircin G. An unusual pediatric case with neurofibromatosis and systemic lupus erythematosus. *Rheumatol Int*. 2012;32(8):2345-2347.

    doi: 10.1007/s00296-011-1966-z

25. Das S. Neurofibromatosis type 1, sarcoidosis, and anterior uveitis: A simple coincidence or coexistence? An interesting case report. *Kerala J Ophthalmol*. 2025;37(1):66-70.

    doi: 10.4103/kjo.kjo_35_23

26. Srivastava P, Gupta S, Bamba C, *et al*. Neurofibromatosis type 1: Clinical characteristics and mutation spectrum in a North Indian cohort. *Heliyon*. 2023;10(1):e23685.

    doi: 10.1016/j.heliyon.2023.e23685

27. Gjorgjievska M, Bozhinovski G, Sukarova-Angelovska E, *et al*. Mutational spectrum and genotype-phenotype correlations in neurofibromatosis type 1 patients from North Macedonia: Identification of ten novel NF1 pathogenic variants. *Balkan Med J*. 2023;40(4):252-261.

    doi: 10.4274/balkanmedj.galenos.2023.2022-12-28

28. Gross AM, Glassberg B, Wolters PL, *et al*. Selumetinib in children with neurofibromatosis type 1 and asymptomatic inoperable plexiform neurofibroma at risk for developing tumor-related morbidity. *Neuro Oncol*. 2022;24(11): 1978-1988.

    doi: 10.1093/neuonc/noac109

29. Campagne O, Yeo KK, Fangusaro J, Stewart CF. Clinical pharmacokinetics and pharmacodynamics of selumetinib. *Clin Pharmacokinet*. 2021;60(3):283-303.

    doi: 10.1007/s40262-020-00967-y