International Journal of Research in Dermatology
Mohamed Z et al. Int J Res Dermatol. 2025 Jul;11(4):308-312
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20251436

Case Report

Neurofibromatosis type 1 with diagnostic value of skin and ocular manifestations

Zainab Mohamed[1]*, Hanan Furjani[2], Farah Eltayyeb[2], Rafea M. Al Ghanem[3]

[1]Department of Dermatology, Qatar Armed Force, Medical Services, Qatar
[2]Department of Ophthalmology, Qatar Armed Force, Medical Services, Qatar
[3]Department of Family Medicine, Qatar Armed Force, Medical Services, Qatar

Received: 26 April 2025
Revised: 02 May 2025
Accepted: 06 May 2025

***Correspondence:**
Dr. Zainab Mohamed,
E-mail: Zainab.mhd.rahma@gmail.com

ABSTRACT

Neurofibromatosis type 1 (NF1) is a genetic mutation - autosomal dominant neurocutaneous condition, with variable clinical expression. The mutation in a gene contains the code for making a protein (Neurofibromin), which acts as tumor suppressor. It is characterized by a pigmentation of skin, non-cancerous (benign) tumors to grow along the nerves in skin, eyes, brain and other body parts. Those tumors and their complications are usually causing a range of symptoms. It is an extremely variable multisystem disease; the progression and severity may differ throughout life in an affected individual as well as in affected family members with the same NF1. This case report presents a 12-year-old boy with a clinical diagnosis of NF1, who was diagnosed initially at the age of two with multiple hyperpigmented macules. He has a positive family history, with similar symptoms in his father and grandfather. Dermatological examination revealed café-au-lait macules (CALMs) on the chest and back, measuring over 1.5 cm, alongside axillary and inguinal freckling. Ophthalmological evaluation showed Lisch nodules in both irises and iris hyperpigmentation. Previous lab tests were normal, and imaging studies, including eyes ultrasounds and brain MRI, revealed no abnormalities. This case illustrates the importance of early cutaneous and ocular findings in the diagnosis of NF1, also Multidisciplinary follow ups are important to detect early systemic complications.

Keywords: Neurofibromatosis type 1, Neurofibromin, Autosomal dominant, Genetic mutation, Café-au-lait macules, Lisch nodules, Axillary freckling

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a genetic mutation-autosomal dominant neurocutaneous condition, in autosomal dominant diseases, where 1 mutated or altered copy of the gene in each body cell is enough to cause diseases. Here 2 copies of the genes (NF1) must be mutated/altered to cause the tumors formation. where clinical criteria for diagnosis may not be fully present until late infancy i.e. child born with 1 mutated gene and the second gene mutate in the cells surrounding the nerves in his/her later life.[1]

NF1 is a genetic disorder characterized by the growth of tumors along the nerves, primarily benign neurofibromas. It is a highly variable multisystem disease, with symptoms and severity differing among affected individuals and their family members. Key clinical manifestations include: (Multiple café au lait macules, Intertriginous freckling, Various types of neurofibromas (cutaneous, subcutaneous, plexiform, and nodular), Distinct ocular signs. Individuals with NF1 may experience learning difficulties, behavioral issues, and challenges in social adaptation. Although optic and non-optic gliomas are more common in this population, most

tend to be benign. However, those with extensive plexiform or deep nodular neurofibromas are at increased risk for malignant peripheral nerve sheath tumors, which typically present at a younger age and carry a poorer prognosis than in the general population. Women with NF1 face a higher risk of breast cancer and increased pregnancy complications.

Hypertension is prevalent among these patients, and NF1-related vasculopathy can lead to stroke or other cardiovascular issues in affected children and young adults. Additionally, skeletal abnormalities like vertebral or tibial dysplasia can cause significant disabilities, while gastrointestinal, endocrine, or pulmonary complications, though less common, can be quite serious.

Overall, NF1 is a complex condition requiring comprehensive management due to its diverse and potentially severe complications.[2-4]

CASE REPORT

History and physical examination

An alert, tall and a good school performing 12-year-old boy, was referred from the family medicine department for further dermatological evaluation. The skin condition began at the age of 2 years, presenting with the gradual appearance of multiple hyperpigmented macules. The patient was previously evaluated by several physicians inside and outside Qatar and was clinically diagnosed with NF1. A skin biopsy was also performed during the earlier evaluations to support the diagnosis.

The patient has a positive family history of NF1, with similar symptoms and signs observed in first-degree relatives, including his father and grandfather.

Dermatological examination revealed multiple CALMs distributed over the chest and back. The lesions vary in size, with several measuring more than 1.5 cm in diameter, and the large café -au-lait patch in left lower aspect of abdomen and left upper thigh, as well as others measuring less. Axillary and inguinal freckling were observed. No involvement with the mucous membranes was noted.

Ophthalmological evaluation showed the presence of Lisch nodules (iris hamartomas) in both eyes, along with areas of iris hyperpigmentation. Those Lisch nodules didn't affect his vision. Visual acuity, fundus examination, visual field, exophthalmometer and ultrasound were all normal.

Previous laboratory investigations, including routine blood tests, were within normal limits. Radiological workup, including multiple X-rays, ultrasounds and brain MRI, showed no abnormalities. No neurological deficits were detected on clinical examination.

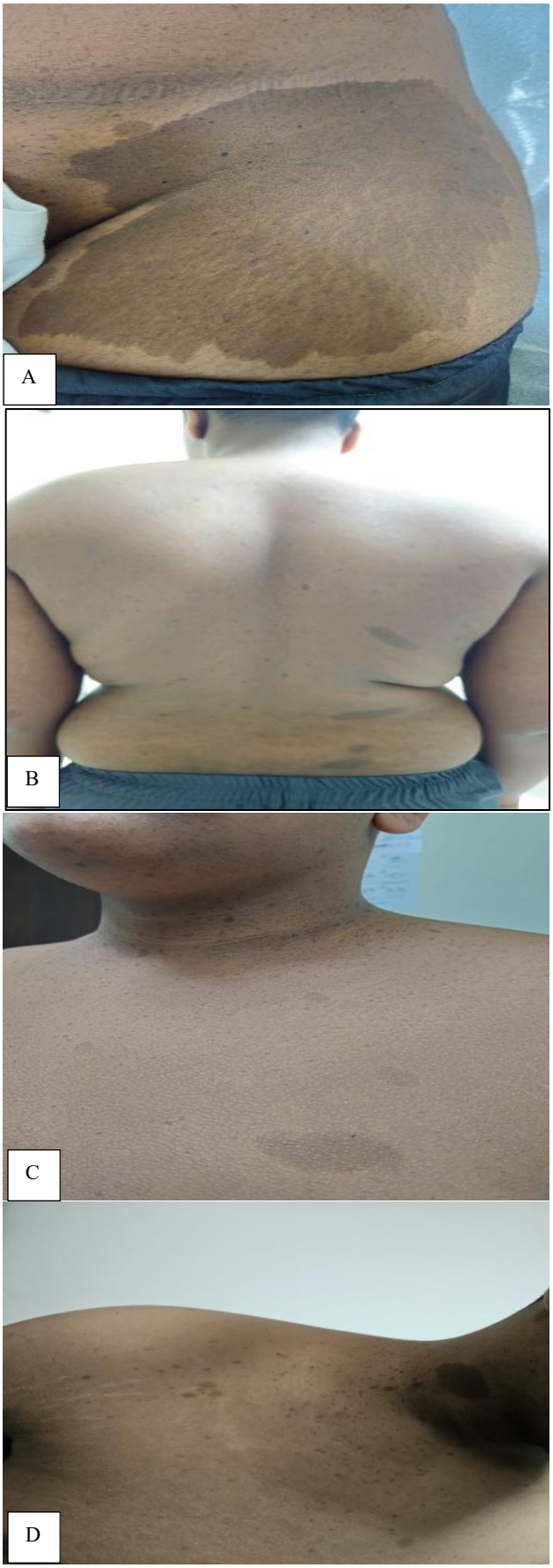

Figure 1 (A-D): Larg patch of CAL, CAL macule and patch in back, patches of CAL and patches of CAL.

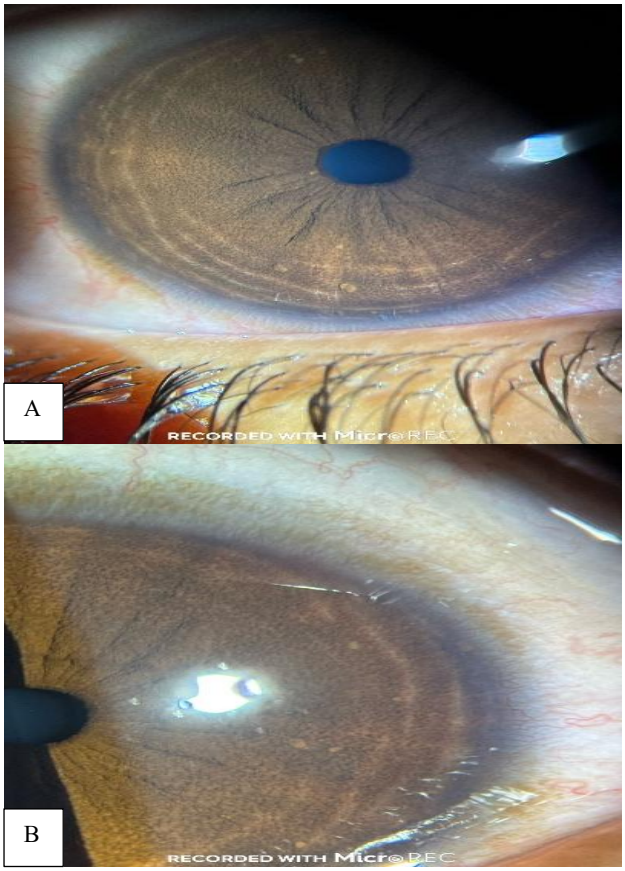

Figure 2 (A and B): Lisch nodules (iris hamartomas) and Lisch nodules (iris hamartomas).

DISCUSSION

This 12 years old boy, presented with some classic features of NF1

Diagnostic criteria met NIH (National institutes of health criteria for NF1) criteria for NF1: >6 CALMs >1.5 cm (confirmed in examination), axillary and inguinal freckling observed, Lisch nodules (iris hamartomas) confirmed in ophthalmological exam and positive family history (father and grandfather with NF1).

Supporting findings were onset of pigmentation at the age of 2-aligns with typical onset of NF1 presentation. Skin biopsy and clinical evaluation-further supports the diagnosis. Normal neurological and radiological exams-suggests no current CNS involvement.

No signs of: Neurofibromas (yet maybe later), optic nerve glioma, skeletal abnormalities or intellectual disability and mucosal involvement or malignancy at this time.

In the present case, a 12-year-old male presented with classical cutaneous and ocular features of NF1, including multiple CALMs exceeding 1.5 cm, axillary and inguinal freckling and Lisch nodules on both irises. These findings meet at least 3 of NIH diagnostic criteria for NF1, supporting the diagnosis. Also, the positive family history with both father and grandfather reinforces the inherited genetic pattern.

Clinical diagnostic criteria for NF1 includes two or more of the following: Six or more CAL macules greater than 5 mm in diameter in prepubertal children and greater than 15 mm post pubertal. Axillary or inguinal freckles (>2 freckles) (if only CAL and freckling are present, one of these two cutaneous manifestations should be bilateral, and Legius syndrome should be considered, though the diagnosis is still likely NF1). Two or more typical neurofibromas or one plexiform neurofibroma. Optic pathway glioma. Two or more iris hamartomas (Lisch nodules), often identified only through slit-lamp examination by an ophthalmologist; or two or more choroidal abnormalities (bright, patchy nodules imaged by optical adherence tomography/near infrared reflectance imaging).[5]

Our findings are consistent with previous literature. According to Riccardi 6 or more CALMs larger than 1.5 cm are the most reliable early diagnostic markers.[6]

According to Huson et al the CAL patches are present in more than 90% and appear in early childhood.[7]

According to Lister nick et al more than 70% of patients over 10 years have Lisch nodules.[8]

According to Ferner et al up to 60% of NF1 patients may not have significant neurological involvement in childhood.[9]

The observed-on examinations are the most common skin manifestation of NF1 and are significant diagnostic indicators. In this case, the presence of several macules larger than 1.5 cm, along with axillary and inguinal freckling, meets the NIH diagnostic criteria for NF1. It is important to note how macule size and distribution can vary widely among patients, as seen here, contributing to variability in clinical presentation.

The positive family history, with the father and grandfather also displaying similar symptoms, highlights the autosomal dominant inheritance pattern of NF1. Genetic counseling may be beneficial for the family to discuss the implications of this hereditary condition.

Ophthalmological findings, particularly the presence of Lisch nodules, further support the NF1 diagnosis. These iris hamartomas are typically asymptomatic but serve as another hallmark feature of the disorder. Their identification is essential during routine ophthalmological evaluations in patients with NF1.

Laboratory tests and radiological evaluations in this case were within normal limits, which is encouraging, as NF1 can be associated with a range of complications, including neurofibromas, cognitive deficits, and more

serious conditions like optic gliomas. The absence of neurological deficits and abnormalities in neuroimaging is a positive aspect and indicates that the patient currently has a stable course of the disease.

NF1 presents with a spectrum of clinical findings that can vary significantly with age and individual circumstances. The earliest indicators of NF1 in children are multiple CAL spots, which may be evident at birth or develop over time, typically increasing in size and number throughout childhood. In adults, these spots often fade and become less noticeable upon clinical examination.

Axillary or inguinal freckles usually appear during childhood or adolescence rather than at birth. In contrast, subcutaneous or cutaneous neurofibromas are rarely observed in young children but tend to manifest with age, primarily in older children, adolescents, and adults. These lesions can be detected through palpation for deeper tumors, while cutaneous lesions may present initially as small papules located on the trunk, extremities, scalp, or face.

The relationship between neurofibromas and hormonal changes is noteworthy; puberty or pregnancy can lead to an increased number of neurofibromas and rapid growth of pre-existing tumors. Plexiform neurofibromas, which are more extensive and invasive, may result in local discomfort or pain and can lead to bony erosion. Rapid growth of neurofibromas may signal potential malignant transformation, a critical consideration in monitoring.

Optic pathway tumors, commonly low-grade pilocytic astrocytomas, can occur in approximately 15-20% of NF1 patients. While these tumors are often asymptomatic, they can present visual symptoms such as asymmetric visual loss or peripheral field defects, particularly in children under six years of age. Gender differences are evident, as females with NF1 have a three-fold increased likelihood of requiring treatment for vision decline compared to males. Regular monitoring for visual difficulties in children and adolescents is essential, as incidental findings on imaging studies may occur in adults.

Lisch nodules and choroidal abnormalities can be observed during fundoscopic examinations, though they require specific techniques for detection, such as using a slit lamp or infrared monochromatic light.[10]

Skeletal abnormalities associated with NF1 include sphenoid bone dysplasia, which may be asymptomatic but can occasionally lead to complications related to herniation. Congenital pseudarthrosis is often present at birth with tibial bowing, and long bones can exhibit thinning and deformity throughout childhood and adolescence, necessitating continuous monitoring.[5]

Scoliosis is another potential concern, with detection in children under ten years linked to a poorer prognosis and a tendency for rapid progression. Conversely, scoliosis identified during adolescence requires monitoring but typically demands less aggressive intervention.

Given the multifaceted nature of NF1, it is crucial to conduct comprehensive assessments, including monitoring blood pressure due to the association with alternative causes of hypertension. Furthermore, head circumference tracking during the first three years of life is advised to identify any concerning growth patterns.

In summary, the variable presentation of NF1 underscores the importance of multidisciplinary management and regular monitoring to address the diverse complications associated with this condition. Continuous assessment and a proactive approach to managing symptoms can enhance the quality of life for individuals affected by NF1.

CONCLUSION

In conclusion, this case emphasizes the fulfils NIH diagnostic features of cutaneous and ocular manifestation of NF1 (without current systemic complications) and the importance of comprehensive evaluations, including dermatological and ophthalmological assessments, to formulate proper management strategies. Continuous follow-up is crucial to monitor potential complications and reassure patients and their families about the nature of the disorder.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Accetturo M, Bartolomeo N, Stella A. In-silico analysis of NF1 missense variants in Clinvar: translating variant predictions into variant interpretation and classification. Int J Mol Sci. 2020;21(3):721.
2. Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated approach to patients with multiple café au lait macules. Dermatol Clin. 2022;40(1):9-23.
3. Al-Farsi FAH, Al-Alyani OBS, Al-Kumzari A, Al-Saadi T. Systemic review and meta-analysis of the intellectual integrity of children with neurofibromatosis type 1. World Neurosurg. 2022;157:69-74.
4. Anderson MK, Johnson M, Thornburg L, Halford Z. A review of selumetinib in the treatment of neurofibromatosis type 1-related plexiform neurofibromas. Ann Pharmacother. 2022;56(6):716-26.
5. Arun D, Gutmann DH. Recent advances in neurofibromatosis type 1. Curr Opin Neurol. 2004;17(2):101-5.

6. Riccardi VM. Neurofibromatosis: Phenotype, Natural History, and Pathogenesis. 2nd ed, Johns Hopkins University Press; 1992.
7. Huson SM, Hughes RAC, Harper PS. Clinical presentation of neurofibromatosis type 1 in children and adolescents. Brain. 1989;112(5):1083-91.
8. Listernick R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. J Pediatr. 1994;125(1):63-6.
9. Ferner RE, Huson SM, Thomas N, Celia M, Harry W, Gareth DE, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007;44(2):81-8.
10. Barnett C, Alon T, Abraham A, Kim RH, McCuaig JM, Kongkham P, et al. Evidence of small-fiber neuropathy in neurofibromatosis type 1. Muscle Nerve. 2019;60(6):673-8.

Cite this article as: Mohamed Z, Furjani H, Eltayyeb F, Al Ghanem RM. Neurofibromatosis type 1 with diagnostic value of skin and ocular manifestations. Int J Res Dermatol 2025;11:308-12.