Type 1 Neurofibromatosis: Adulthood Diagnosis and New Variant

Neurofibromatose Tipo 1: Diagnóstico em Idade Adulta e Nova Variante

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Palavras-chave: Manchas Café com Leite/genética; Neurofibromatose 1/diagnóstico; Neurofibromatose 1/genética.

A 57-year-old female, with history of hypertension and uterine leiomyoma. Referred to Internal Medicine due to anaemia. On evaluation, numerous fibrotic, mobile nodular lesions were observed, mostly on the trunk, abdomen, and back, with two café-au-lait spots (CAL) (Fig.1). The patient has no growth or cognitive abnormalities, Lisch nodules, or other neoplasms. She reported similar lesions in her deceased father and paternal aunt, without a confirmed genetic diagnosis, and in her brother. Her daughter is healthy, without CAL spots or neurofibromas (Fig.2).

Molecular testing identified a likely pathogenic variant c.7807-1_7810dup p. (Thr2604Argfs*5) in heterozygosity in the neurofibromatosis type 1 (*NF1*) gene, not previously described in literature, gnomAD, or ClinVar, but reported as likely pathogenic in the Franklyn NF1 database. Histology of an abdominal

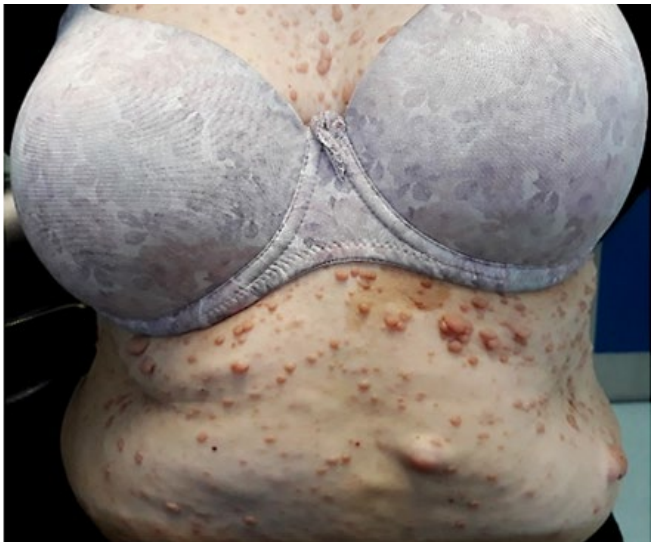

Figure 1: Fibrotic, mobile nodular lesions with café-au-lait spots, in a patient with Neurofibromatosis type 1 (patient-authorized image).

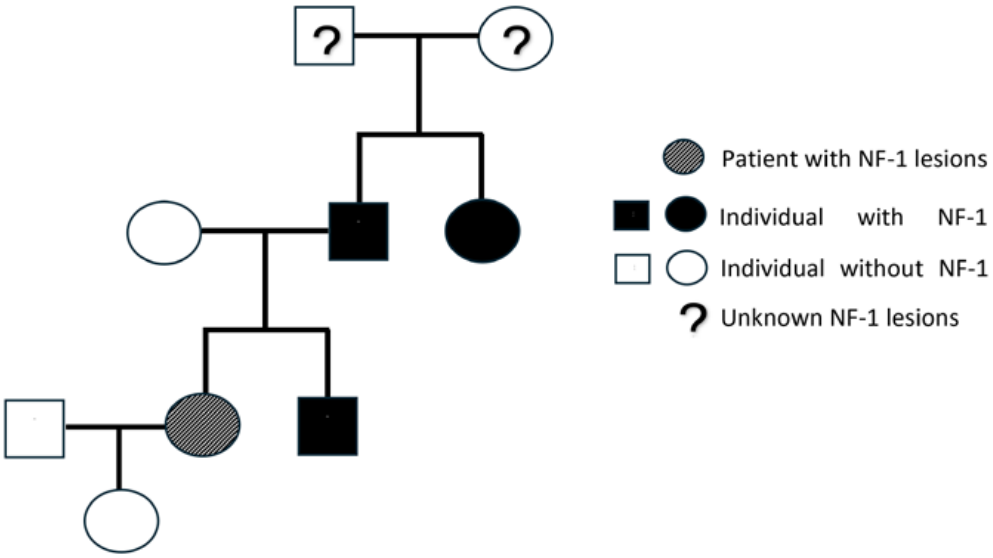

Figure 2: Genogram - Father, paternal aunt and brother with the same lesions as the patient.
NF-1: neurofibromatosis type 1.

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nodule was consistent with a fibrous melanotic nevus. Further evaluation showed no evidence of additional lesions or abnormalities. She continues regular oncologic surveillance, referred for surgery if neurofibromas become symptomatic. Iron deficiency anaemia resolved with oral supplementation, unrelated with the disorder.

NF1 is an autosomal dominant disorder caused by mutations in the *NF1* gene, which encodes neurofibromin, a tumour suppressor gene produced in nerve cells, oligodendrocytes, and Schwann cells – gene deficiency leads to AKT/mTOR and Raf/MEK/ERK pathways' activation and growth of neurofibromas along the nerves.[1] It can arise as a *de novo* mutation in 40% of cases.[2] It results in a broad spectrum of manifestations, with complete penetrance but variable expression.[3] It has a prevalence of 1/1900 to 1/3500, typically diagnosed during childhood. In some, signs are only detected in adulthood due to their indolence.[4]

The increased occurrence of malignant and cardiovascular diseases associates this with a reduction in overall survival.[4,5] – This diagnosis has prognostic implications. It is also relevant due to the discovery of a new potentially pathogenic variant. A cure for NF1 has not been found; emerging experimental treatments involve the modulation of the signalling pathways involving neurofibromin.[2] ■

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PFS, MS, ATR - All the authors contributed equally to this work.
All authors approved the final version to be published.

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PFS, MS, ATR - Todos os autores contribuíram igualmente para este trabalho.
Todos os autores aprovaram a versão final a ser publicada.

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