

## Case Reports

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# Multiple glomus tumor in a patient with neurofibromatosis type 1: a case report and literature review

*Tumor glômico múltiplo em paciente com neurofibromatose tipo 1: relato de caso e revisão de literatura*

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## ABSTRACT

Neurofibromatosis type I (NF1) is an autosomal dominant disease, with an incidence of 1/2,500–3,000 births and a prevalence of approximately 1/4,000–5,000 individuals. Genetic mutations in the NF1 gene cause it, affecting neural and skin tissues. Glomus tumor is a benign neoplasm originating from the glomus, a neuromyoatrial structure of the skin present at the fingertips and involved in thermoregulation. The literature historically considered these tumors isolated and sporadic, but some studies have proved a relationship with neurofibromatosis type I. Thus, patients with neurofibromatosis type 1 should be investigated. The case report provides additional support for the notion that NF1 has a risk associated with multiple glomus tumors.

**Keywords:** Glomus Tumor; Association; Case Reports; Neoplasms; Neurofibromatoses

## RESUMO

*Neurofibromatose tipo I (NF1) é uma doença autossômica dominante, com incidência de 1/2.500-3.000 nascimentos e prevalência de aproximadamente 1/4.000-5.000 indivíduos; é causada por mutações genéticas no gene NF1, que afetam tecidos neurais e cutâneos. Tumor glômico é uma neoplasia benigna originada do glomo, uma estrutura neuromioatrial da pele presente nas pontas dos dedos e envolvida na termorregulação. São considerados historicamente tumores isolados esporádicos, porém existem estudos que comprovam sua relação com a neurofibromatose tipo I. Pacientes com neurofibromatose tipo 1 devem ser investigados. O relato de caso fornece suporte adicional à noção de que NF1 tem um risco associado a múltiplos tumores glômicos.*

**Palavras-chave:** Tumor Glômico; Associação; Relatos de Casos; Neoplasias; Neurofibromatoses

## INTRODUCTION

Glomus tumors are extremely painful benign tumors of the glomus body, a neuromyoarterial structure that exists in high concentrations in the fingertips, and is involved in thermoregulation. Glomus tumors are usually solitary and often arise in a subungual location, although multifocal disease and non-subungual presentation are not uncommon. They occur more commonly in women and usually in the fourth decade of life.<sup>1</sup> Although the true incidence of glomus tumors is unknown, they represent less than 2% of primary hand tumors.<sup>2</sup>

Historically, they have been considered isolated sporadic tumors, not associated with other disease processes. However, multiple case reports, a molecular genetics research, and an epidemiologic study have confirmed that neurofibromatosis type I is associated with glomus tumors.<sup>1</sup>

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder, with an incidence of 1/2,500–3,000 births and a prevalence of approximately 1/4,000–5,000 individuals.<sup>3,4</sup> It is caused by mutations in the NF1 tumor suppressor gene, located on chromosome 17 (17q11.2), which encodes neurofibromin (nf), a protein able to downregulate the Ras-Raf/MAPK signaling pathway that activates cell proliferation. Mutations of the NF1 gene result in function alteration or loss of negative regulator of growth and cellular differentiation of nf. It leads to uncontrolled cell proliferation and an increased risk of developing cancer.<sup>4,5</sup>

### CASE REPORT

A 26-year-old woman with NF1 was assisted at our institution complaining of severe pain in the subungual region of the fifth right finger, on the hyponychium and the lateral nail fold of the third left finger, and the subungual region of the left hallux.

Clinically, the fifth right finger presented longitudinal erythronychia, with purple color and local pain in the proximal nail fold (Figures 1 and 3). The examination of the third left finger was normal, while in the left hallux, we noticed a purple tumor on the middle of the nail bed (Figure 2).

She presented the triad of Carroll (severe pain, point tenderness, and cold sensitivity) in all fingers.

A high-frequency ultrasound showed a 6 mm tumor on the fifth right subungual finger.

After troncular anesthesia, an oblique incision was made in the lateral portion on both sides of the proximal nail fold,

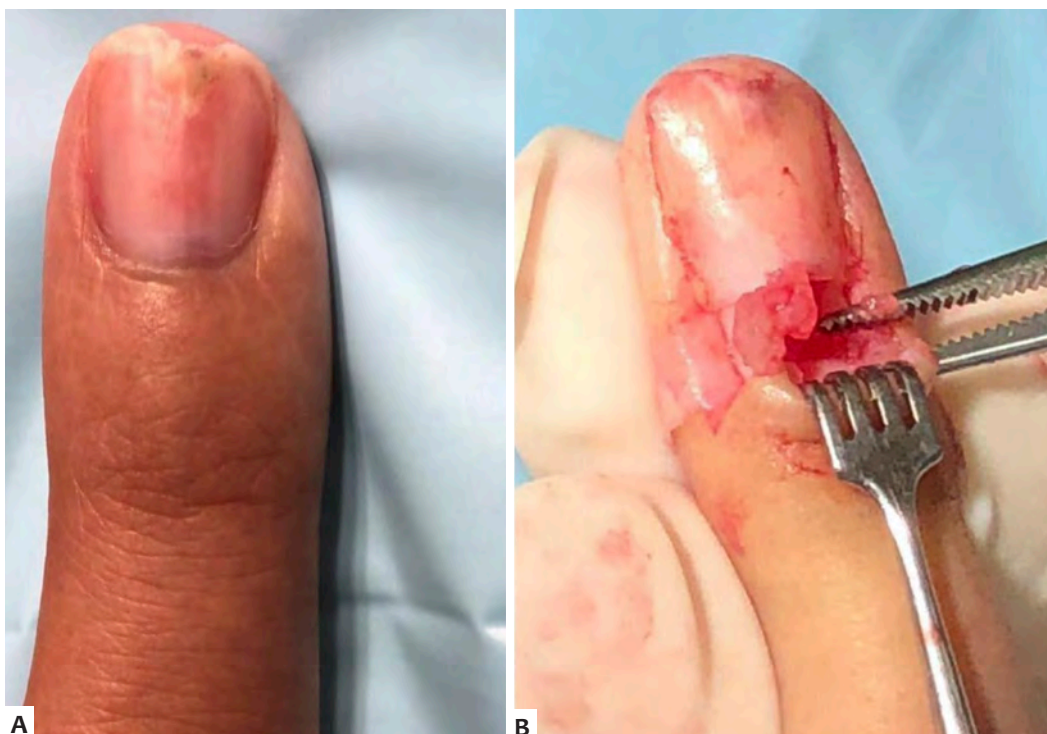
exposing the nail matrix. We conducted the avulsion of the nail and incision in the nail bed, visualizing a reddish tumor, easily detached by divulsion using mosquito forceps. Histological examination of the tumor confirmed the diagnosis of glomus tumor.

### DISCUSSION

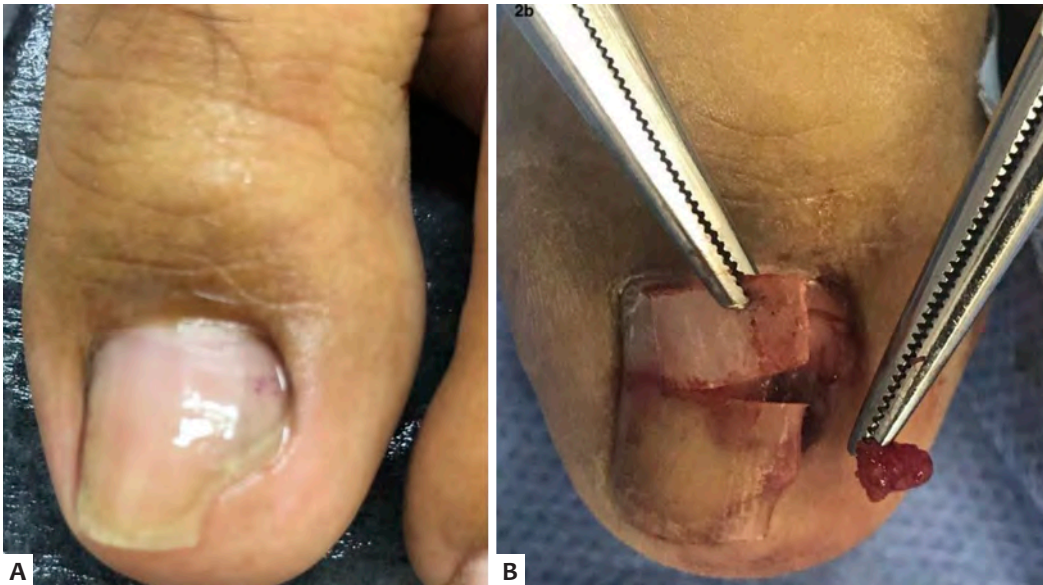
Glomus tumors, usually present in the fingers and toes, are benign tumors that develop from cells that resemble the modified smooth muscle cells of the glomus apparatus.<sup>6</sup> NF1, an autosomal dominant inherited disorder, is caused by mutations of the NF1 gene located on chromosome 17. The protein encoded by the NF1 gene, neurofibromin, acts as a tumor suppressor. Patients with NF1 lose neurofibromin expression, which leads to increased cell proliferation associated with protein kinase, with a propensity to develop many different types of tumors.<sup>7</sup>

With four glomus tumors excised, the present case indicates, together with some previously reported cases, that there is an association between glomus tumors and NF1.

In 1938, Klaber provided the first report of a glomus tumor arising in a patient with neurofibromatosis.<sup>8</sup> The literature no longer contains reports of glomus tumors in patients with neurofibromatosis until 1995, when Sawada et al.<sup>3</sup> reported three patients with neurofibromatosis type I and subungual glomus tumors. Between 1995 and 2013, another 13 case reports described glomus tumors arising in the setting of neurofibromatosis type I. Although many of the authors speculated about the possibility of an association, it was not confirmed until 2009,<sup>1</sup>



**FIGURE 1:** A - Longitudinal erythronychia in the fifth right finger and its proximal nail fold, with a purplish color. B - Visualization of the tumor during surgery



**FIGURE 2:** A - Glomus tumor in the hallux, clinical aspect of the nail before surgery. The patient cut the nail to improve the pain. B - Visualization of the tumor during surgery



**FIGURE 3:** Erythematous-wine color on the side of the finger with pain on palpation; the glomus tumor was removed with surgery

when Brems et al.<sup>9</sup> firmly established a causal relationship between NF1 and glomus tumors. Glomus tumors associated with NF1 exhibit biallelic inactivation of the NF1 gene; thus, seven of the 12 tumors assessed harbored gene and somatic mutations, while two sporadic glomus tumors did not present abnormalities in the NF1 gene.

In 2013, Harrison et al.<sup>2</sup> conducted an epidemiological case-control study comparing a cohort of patients undergoing excision of a glomus tumor with a similar cohort of patients who underwent excision of other benign hand injuries. The study found that 29% of patients undergoing excision of the glomus tumor had a diagnosis of neurofibromatosis, while none of the patients in the control cohort had the disorder.

Most glomus tumors are unique. It is improbable that there will be synchronous tumors in adjacent fingers, as in the present case. However, in a patient with NF1, the risk of glomus tumors is increased. As this case exemplifies, the diagnosis of multifocal glomus tumors should be considered in these patients, especially when the classic triad of clinical features (spontaneous paroxysmal pain, point tenderness, and hypersensitivity to cold) is present. Most are located in the subungual area. Delayed diagnosis and treatment can lead to unnecessary debilitation in such patients.<sup>10</sup>

### CONCLUSION

The case report provides additional support for the concept that NF1 has a risk associated with multiple glomus tumors. For dermatologists who manage patients with NF1, knowing this association can facilitate early diagnosis and appropriate treatment. ●

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