Subungual glomus tumors: Underrecognized clinical findings in neurofibromatosis 1

To the Editor: Wilson et al[1] have written a detailed review on the genetics, diagnosis, and treatment of neurofibromatosis type 1 (NF1). They highlight that the incidence of NF1 is 1 in 2500 persons, making it the most common neurocutaneous syndrome. They stress the importance of early diagnosis for the management of neoplasms. Disease pathogenesis results from loss-of-function mutations in the *NF1* gene, producing a defective neurofibromin protein, and subsequent activation of the RAS signaling pathway. Targeted therapies, including mTOR, tyrosine kinase, and RAS inhibitors, are discussed. Wilson et al list modified diagnostic criteria and provide an algorithm for monitoring patients with NF1. There is one line on glomus tumors mentioning a 5% prevalence and subungual location in patients with NF1. We would like to emphasize that glomus tumors are important clinical findings in patients with NF1, causing significant morbidity, and may be important clues to the diagnosis of this neurocutaneous syndrome.

Glomus tumors are benign tumors commonly localized to the fingertips, particularly the subungual region. They originate from the glomus body, a neuro-myo-arterial structure that regulates vascular flow and temperature. The classic triad is pinpoint tenderness, severe pain, and cold hypersensitivity, which may not be present in all patients. Physical examination of the nail may show longitudinal erythronychia or a bluish nodule seen through the nail plate.[2] X-ray images may show bony erosions, with ultrasonography and magnetic resonance imaging showing smaller tumors. Excision with histopathology, either with a transungual or lateral subperiosteal approach, is necessary for the definitive diagnosis, treatment, and relief of symptoms.

The association between glomus tumors and NF1 was first reported in 1938.[3] In 2009, NF1 mutations on both alleles were found in glomus cells from these tumors. Neurofibromin expression is absent in NF1-associated glomus tumors and is present in sporadic tumors. In a case series of 42 histopathologically confirmed glomus tumors, 6 of 34 patients (17.7%) were diagnosed with NF1, and 12 glomus tumors were present in these patients (28.6% of all glomus tumors). Recurrence was more common in patients with NF1 (33.3%) compared to patients with sporadic tumors (7.1%). In addition, multifocal tumors were more frequent in NF1 (16.7%) versus sporadic tumors (7.1%).[4] In another case series of 21 excised glomus tumors, 6 of 21 patients were diagnosed with neurofibromatosis. In a control cohort of 200 patients who underwent ganglion cyst excisions, there were no patients with neurofibromatosis. The odds ratio of neurofibromatosis in association with a glomus tumor versus controls was 168:1.[5]

Physicians should be familiar with the clinical presentation of a subungual glomus tumor. After diagnosis confirmation, a complete medical, surgical, and family history, as well as a targeted review of systems for NF1, should be performed. The presence of multiple, recurrent, or multifocal glomus tumors merits a thorough workup for NF1. Furthermore, because glomus tumors may cause significant pain and delayed diagnosis is commonplace, patients with NF1 should be routinely screened for these tumors. Finally, because multiple glomus tumors are exceedingly rare in the general population, we propose that this finding be incorporated into the diagnostic criteria for NF1.

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Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

Reprints not available from the authors.

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https://doi.org/10.1016/j.jaad.2020.08.129