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# Glomus tumors in individuals with neurofibromatosis type 1

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**Background:** Glomus tumors have recently been reported in individuals with the neurofibromatosis type 1 (NF1) cancer disposition syndrome. We compare the clinical and molecular features of these painful hamartomas in a series of sporadic and NF1-associated cases.

**Objective:** We sought to evaluate the association of NF1 with glomus tumors and to compare NF1-associated glomus tumors with sporadic glomus tumors.

**Methods:** We conducted a retrospective cohort study of all individuals with a histopathologic diagnosis of glomus tumor at a large tertiary care center from January 1998 to January 2013. Charts were reviewed for a coexisting diagnosis of NF1.

**Results:** A total of 42 glomus tumors were identified in 34 individuals. Twelve (28.6%) were found in 6 patients with NF1. In 28 individuals with 30 sporadic tumors, there was no coexisting medical condition. Although multifocal tumors (16.7%) and tumor recurrence (33.3%) were more common in association with NF1, these trends did not reach statistical significance. NF1-associated glomus tumors exhibited no neurofibromin immunoreactivity, whereas their sporadic counterparts retained neurofibromin expression.

**Limitations:** The retrospective design resulted in incomplete data capture.

**Conclusions:** Detection of glomus tumors should raise suspicion for a concurrent diagnosis of NF1. (J Am Acad Dermatol 2014;71:44-8.)

**Key words:** glomus tumor; neurofibromatosis; neurofibromatosis type 1; neurofibromin; tumor disposition syndrome.

Little is known about the pathogenesis of glomus tumors and no causative genetic mutations are identified. Insights into possible origins come from reports that individuals with neurofibromatosis type 1 (NF1) are prone to develop these tumors.<sup>1-7</sup> Children and adults with NF1 are predisposed to a wide variety of benign and malignant tumors, including brain tumors (optic pathway gliomas, malignant astrocytomas), peripheral nerve sheath tumors (neurofibromas, malignant peripheral nerve sheath tumors), pheochromocytomas, leukemia, and rhabdomyosarcoma.<sup>8,9</sup> NF1 is caused by germline mutations in the *NF1* tumor suppressor

gene (OMIM 613113); tumors form after somatic inactivation of the 1 remaining functional *NF1* allele.<sup>9,10</sup>

Although the association between glomus tumors and NF1 was first noted in 1938,<sup>1</sup> the relationship was conclusively established with the demonstration that NF1-associated glomus tumors exhibit biallelic inactivation of the *NF1* gene.<sup>11</sup>

To define the clinical and molecular characteristics of glomus tumors arising in adults with NF1 relative to those found in the general population, we conducted a retrospective chart review study of individuals seen in a large tertiary care center.

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Dr Bayliss is currently conducting a study with Scioderm for epidermolysis bullosa.

Conflicts of interest: None declared.

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## METHODS

### Subjects

All individuals who underwent excision of a glomus tumor between January 1998 and January 2013 were identified after a pathology database (CO-PATH) search. Electronic records were reviewed for each individual and the presence or absence of a diagnosis of NF1 was recorded, using National Institutes of Health Consensus Development Conference criteria.<sup>12</sup> Sex, age at the time of glomus tumor excision, and the number and location of glomus tumors were recorded. This study was performed under an approved human studies protocol at the Washington University School of Medicine, Saint Louis, MO.

### Immunohistochemistry

Formalin-fixed, paraffin-embedded blocks containing histopathologically verified glomus tumors were sectioned and processed for neurofibromin immunohistochemistry and 3, 3'-diaminobenzidine development as previously published.<sup>13</sup> Representative photomicrographs were acquired on a microscope (Eclipse E600, Nikon Corp, Tokyo, Japan) equipped with a Leica EC3 optical camera and Leica Application Suite 2.10 (Leica Microsystems, Wetzlar, Germany). Normal-appearing human skin was used as an internal positive control for neurofibromin staining.

### Statistical analysis

Descriptive statistics were calculated to characterize the study cohort. Fisher exact test was used to identify differences between NF1-associated glomus tumors and sporadic glomus tumors. Significance level was set at  $P = .05$ . A 1-way  $\chi^2$  analysis test was used to compare observed individuals with NF1 and glomus tumors to expected individuals with NF1 (using 1/3000 NF1 incidence).<sup>14</sup> Statistical analyses were performed using statistical software (SAS, Version 9.2, SAS Institute Inc, Cary, NC).

## RESULTS

A total of 42 histopathologically confirmed glomus tumors were identified in 34 individuals during the 15-year study period. Six of 34 patients (17.7%) also carried a diagnosis of NF1, none of

whom were related. Twelve glomus tumors were found in the 6 individuals with NF1, representing 28.6% of the total glomus tumors in this series. One patient with NF1 had multiple glomus tumors ( $n = 7$ ); another had a histopathologic diagnosis of neurofibroma and glomus tumor within the same surgical specimen (Fig 1).

### CAPSULE SUMMARY

- Glomus tumors may occur as part of the neurofibromatosis type 1 cancer disposition syndrome.
- We confirmed absence of neurofibromin in neurofibromatosis type 1-associated glomus tumors; neurofibromin expression was retained in sporadic glomus tumors.
- Detection of glomus tumors should raise suspicion for a concurrent diagnosis of neurofibromatosis type 1.

The demographic characteristics are shown in Table I. No associations with medical conditions other than NF1 were found. Females were slightly more likely to have glomus tumors in the general population (55.9%) and in the context of NF1 (66.7%). The average age at surgical excision was 45 years in both the NF1-related and sporadic tumor cohorts; affected individuals reported pain for as many as 15 years before the diagnosis of glomus tumor. Recurrence was noted in 2

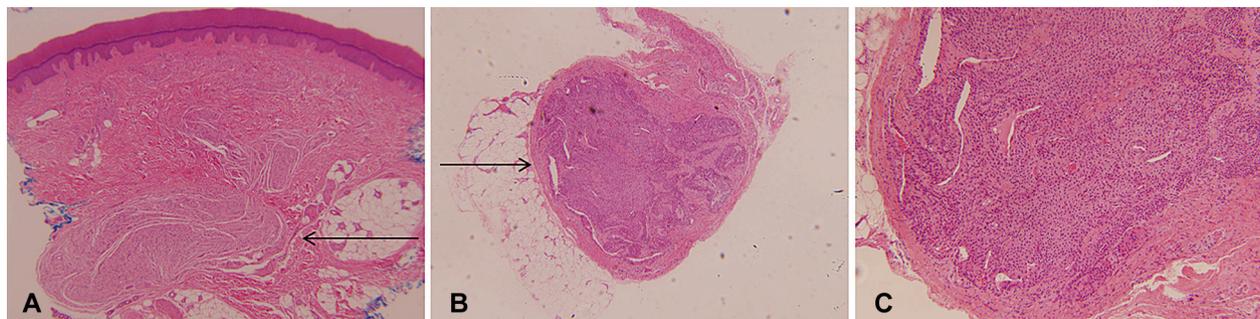
NF1 cases (33.3%) and in 2 sporadic glomus tumor cases (7.1%). Multifocal tumors were found in 1 NF1 case (16.7%) and in 2 sporadic glomus tumor cases (7.1%).

Tumor location was recorded (Table II). Of all the glomus tumors, 66.7% involved the hand, whereas 33.3% were located elsewhere on the body, including the toes, eyelids, extremities, and ear canal. Of the glomus tumors found in individuals with NF1, 83% were located on the hand (10/12 tumors), and 16.6% were found elsewhere on the body, including the left second toe and right thigh (2/12 tumors). They were approximately evenly distributed among the 5 digits, with 25% involving the thumb. In contrast, sporadic glomus tumors were more commonly located on the index finger (6/30 tumors; 20%) and small finger (6/30 tumors; 20%); however, these site predilections were not statistically significant. Glomus tumors were more likely to be located on the left side of body in both cohorts ( $P = .12$ ).

Representative glomus tumors from both cohorts were analyzed for *NF1* gene expression using an antibody specific for the neurofibromin protein. Whereas no neurofibromin expression was detected in the glomus tumors from individuals with NF1, the sporadic glomus tumors retained expression of the neurofibromin protein (Fig 2).

## DISCUSSION

The findings from this study highlight several important issues.



**Fig 1.** A coexisting neurofibroma and glomus tumor. **A**, Superficial portion of a skin specimen from the right small finger shows large fascicles of spindle cells in dermis (neurofibroma). **B**, The deep portion of the same skin specimen shows the glomus tumor interwoven with strands of neurofibroma. **C**, Characteristic features of the glomus tumor included thin-walled vessels surrounded by rows of uniform cells with round dark nuclei (glomus cells). (A to C, Hematoxylin-eosin stain; original magnifications: **A** and **B**,  $\times 4$ ; **C**,  $\times 10$ .)

**Table I.** Summary of demographic characteristics of individuals given the diagnosis of glomus tumors, broken down into 2 cohorts: neurofibromatosis type 1–associated versus sporadic

Feature	Glomus tumor			P value
	Total	NF1	Sporadic	
Patients, N (%)	34	6 (17.7)	28 (82.4)	
Gender, N (%)	15 M (44.1) 19 F (55.9)	2 M (33.3) 4 F (66.7)	13 M (46.4) 15 F (53.6)	.67
Number (%)	42	12 (28.6)	30 (71.4)	
Average age at surgery, y, N (minimum, maximum)	44.8 (12, 70)	45.2 (34, 67)	44.7 (12, 70)	.62
Patients with multifocal tumors, N (%)	3 (8.8)	1 (16.7)	2 (7.1)	.45
Patients with recurrence, N (%)	4 (11.8)	2 (33.3)	2 (7.1)	.13

F, Female; M, male; NF1, neurofibromatosis type 1.

**Table II.** Summary of location of glomus tumors, broken down into 2 cohorts: neurofibromatosis type 1–associated versus sporadic

Location of tumor, N (%)	Glomus tumor			P value
	Total	NF1	Sporadic	
F1 (thumb)	4 (9.5)	3 (25.0)	1 (3.3)	.12
F2 (index)	7 (16.7)	1 (8.3)	6 (20.0)	.36
F3 (long)	4 (9.5)	2 (16.7)	2 (6.7)	.60
F4 (ring)	5 (11.9)	2 (16.7)	3 (10.0)	1.00
F5 (small)	8 (19.1)	2 (16.7)	6 (20.0)	.67
F totals	28 (66.7)	10 (83.3)	18 (60.0)	.28
Toes	2 (4.8)	1 (8.3)	1 (3.3)	.49
Other	12 (28.6)	1 (8.3)	11 (36.7)	.13
L and R	25 L (59.5) 17 R (40.5)	7 L (58.3) 5 R (41.7)	18 L (60.0) 12 R (40.0)	.12

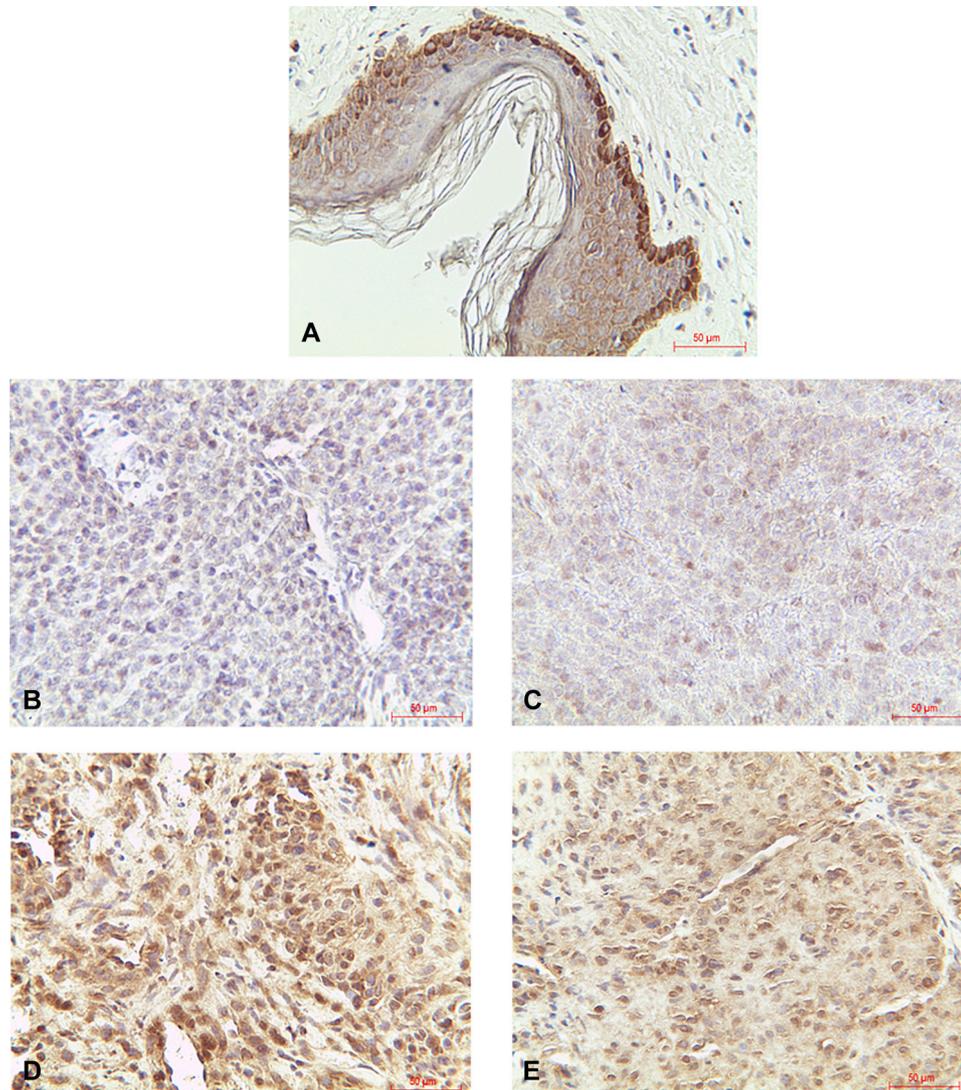
F, Finger; L, left; NF1, neurofibromatosis type 1; R, right.

First, glomus tumors are rare in the general population, representing less than 2% of primary hand tumors (the true incidence of glomus tumors is unknown).<sup>6</sup> A predilection for regions exposed to temperature extremes is reflected by their predominance on the hands. Similar to previous studies, the

majority involved the fingers in both sporadic and NF1-associated cases.<sup>6,15,16</sup> The exact distribution of glomus tumors on the 5 digits varies slightly from study to study, with a slight increase (25%) of tumors affecting the thumb in this study. They are typically managed by surgical excision, but many recur years later. Although there was a trend toward more frequent recurrence in individuals with NF1, this was not statistically significant.

Second, glomus tumors are overrepresented in individuals with NF1. Recent reports have established a clear cause-and-effect relationship with NF1. Previous studies have estimated that 5% of individuals with NF1 harbor a glomus tumor.<sup>16</sup> They may be underdiagnosed by clinicians caring for patients with NF1. Routine screening for these tumors is not commonplace in most NF1 clinical programs, and individuals with NF1 may experience pain from a glomus tumor for up to 20 years before diagnosis.<sup>6</sup> The relative rarity of these tumors, their small size, and their variable presentation often results in misdiagnosis and delayed treatment.

Conversely, dermatologists may not consider NF1 as a comorbid condition when evaluating individuals



**Fig 2.** Glomus tumor. Neurofibromin expression in sporadic and neurofibromatosis type 1 (NF1)-associated glomus tumors. **A**, Neurofibromin expression is detected in normal-appearing human skin. Although no neurofibromin expression was found in 2 representative NF1-associated glomus tumors (**B** and **C**), robust expression was detected in 2 representative sporadic glomus tumors (**D** and **E**). Scale bars, 50  $\mu\text{m}$ . (**A** to **E**, Original magnifications:  $\times 200$ .)

presenting with glomus tumors. The detection of 6 individuals with NF1 in a series of 34 cases of glomus tumor is far greater than expected based on a NF1 prevalence of 1:3000 in the general population ( $P < .001$ ). Given the propensity of these individuals to develop other more serious medical complications, including malignant brain cancers and internal neurofibromas, dermatologists treating individuals with glomus tumors should evaluate for clinical features of NF1. The co-occurrence of a neurofibroma in 1 glomus tumor specimen highlights the need to consider a diagnosis of NF1.

Third, the addition of glomus tumors to the list of tumors associated with the NF1 cancer predisposition

syndrome may provide insights into the molecular pathogenesis of tumors arising in the general population. Elegant studies by Brems et al<sup>11</sup> have firmly established a causative relationship between NF1 and glomus tumors: NF1-associated glomus tumors exhibit biallelic inactivation of the *NF1* gene, such that 7 of 12 tumors studied harbored both germline and somatic *NF1* gene mutations, whereas 2 sporadic glomus tumors had no *NF1* gene abnormalities. Stewart et al<sup>16</sup> further demonstrated that mitotic recombination involving the *NF1* locus was the most likely cause for loss of *NF1* gene expression. Consistent with these observations, we demonstrate that neurofibromin protein expression

is absent in the NF1-associated cases, but retained in the sporadic tumors.

Although NF1-associated and sporadic glomus tumors are similar in terms of patient sex, age at presentation, multifocality, and recurrence, they differ in their underlying molecular pathogenesis. Recent studies have shown that NF1-associated and sporadic brain tumors have different molecular alterations that converge on the same growth control pathway.<sup>17</sup> Whereas NF1-associated pilocytic astrocytomas harbor biallelic *NF1* gene inactivation,<sup>13</sup> their sporadic counterparts have a genetic alteration in which the *BRAF* (v-raf murine sarcoma viral oncogene homolog B) gene is fused to a gene of unknown function.<sup>18</sup> Importantly, both genetic changes lead to hyperactivation of a central growth regulatory pathway (mammalian target of rapamycin) relevant to therapeutic drug targeting.<sup>17</sup> Future studies focused on potential shared signaling pathways may yield new insights into the molecular drivers of sporadic glomus tumors.

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