

ELECTRONIC LETTER

Multifocal glomus tumours of the fingers in two patients with neurofibromatosis type 1

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A glomus tumour of the finger is a benign tumour that develops from the neuromyoarterial elements of the glomus body, which is a specialised arteriovenous anastomosis involved in thermoregulation. In this structure the arterioles that connect with venules have a thick layer of concentrically arranged epitheloid smooth muscle cells. Contraction of the layer of smooth muscle cells results in closure of the arteriovenous anastomosis and this will force blood to flow through the capillary network. Control of the function of the arteriovenous anastomoses is mainly neural. Most glomus tumours are localised in the distal phalanx. It is a small tumour with a subungual or pulpar localisation and with typical symptoms consisting of the triad pain, cold intolerance, and very localised tenderness.¹ Most cases of phalangeal glomus tumours are solitary. A related condition called multiple glomuvenous malformations of the skin shows autosomal dominant inheritance² and is linked to the chromosome 1p21-22 region.³ The abnormalities in the skin consist of cutaneous venous malformations with smooth muscle-like glomus cells. Recently the gene involved in this familial condition has been cloned and named glomulin.⁴ Glomuvenous malformations of the skin are clinically and aetiologically different from the sporadic glomus tumours of the distal phalanx. The jugular glomus tumours seen in familial paragangliomas originate in a structure of a different type from the glomus bodies of the fingers. The carotid and jugular bodies have a different histology; most are chemoreceptors and they consist of a spherical conglomeration of cells and small blood vessels. Therefore, they are also called glomera.

The association of glomus tumours of the fingers with neurofibromatosis type 1 (NF1) is rarely observed with only 12 cases having been reported previously.⁵⁻⁷

CASE REPORTS

Case 1

A 53 year old female presented with extreme pain in the pulpa of the right ring finger and the left middle finger. The pain had been present for more than one year. She had been diagnosed with neurofibromatosis type 1 (NF1) based on clinical features (more than six cutaneous café au lait spots, iris Lisch nodules, axillary freckling, cutaneous neurofibromas, and first degree relatives with NF1). Several soft tissue tumours in the face had been removed and diagnosed histologically as neurofibromas. Despite numerous cutaneous soft tissue nodules spread all over her body, there were no nodules found at the specific painful region of the affected fingers. Love's test was positive. Transillumination and radiographs were negative.

Under local anaesthesia both pulpa were explored and a small nodule was found in each one. Histological examination of the excised nodules showed a typical glomus tumour in each (fig 1).

Postoperative follow up was uneventful and all symptoms disappeared completely immediately postoperatively. At 18 months follow up, there was no evidence of recurrence. A cytogenetic study with fluorescence in situ hybridisation with

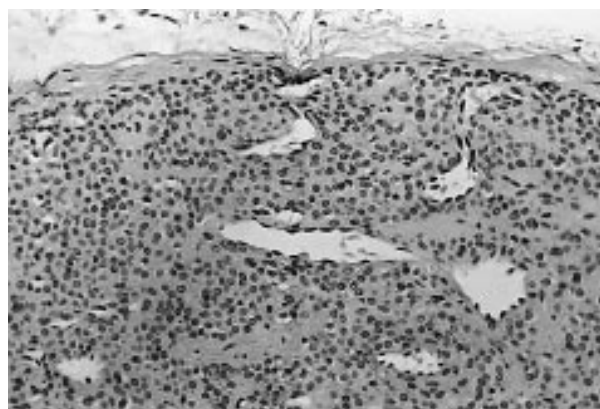


Figure 1 Encapsulated glomus tumour, characterised by solid nests of cells interrupted by vascular channels (H & E stain).

NF1 gene specific probes excluded a total *NF1* gene deletion in peripheral blood lymphocytes in this patient.

Case 2

The diagnosis of NF1 in this 35 year old man was based on the presence of multiple (more than six) café au lait spots, cutaneous neurofibromas, axillary freckling, the presence of iris Lisch nodules, and a first degree relative with NF1. He complained of extreme pain in the third and fourth finger of his right hand, dorsally at the base of the nail. A slight reddish spot was present at this location. Love's test was positive. The pain could be provoked by exposure to cold. In fact the patient worked as a grocery store clerk and working in a cold storage room triggered severe pain attacks in the third and fourth finger of his right hand.

Both pulpa were explored under local anaesthesia. A 1.5 mm diameter tumour was found in both nail roots. Histological examination confirmed the diagnosis of glomus tumour. The symptoms disappeared immediately. No genetic studies have been performed yet in this patient.

DISCUSSION

In this letter, we describe two patients with NF1 and multiple phalangeal glomus tumours. Phalangeal glomus tumours are usually solitary and the association with NF1 has only rarely been reported.⁵⁻⁷ The occurrence of multiple glomus tumours in the nail beds is extremely rare in the general population. However, several published cases of NF1 patients (at least five)^{6,7} and the two patients reported here had multiple glomus tumours. The occurrence of multiple phalangeal glomus tumours in several patients with NF1 suggests that

Abbreviations: NF1, neurofibromatosis type 1; NCSC, neural crest stem cells; SMA, smooth muscle actin

this is not an incidental association but that NF1 patients have an increased, albeit low, incidence of glomus tumours. Moreover, it is possible that glomus tumours of the pulpa are not always diagnosed in NF1 patients because the symptoms might be attributed to the presence of cutaneous neurofibromas in the same region and resection of the superficial nodules (cutaneous neurofibromas) is insufficient to diagnose and resolve the problem. Therefore, it is important to be aware of the possibility of glomus tumours in NF1 patients with pain in the fingers because surgical intervention to remove the glomus tumour cures the pain.

Neurofibromas in NF1 patients are composed of fibroblasts, mast cells, perineural cells, axons, and Schwann cells. It has been shown that the Schwann cells are the tumoral cells in neurofibromas⁸⁻⁹ and it is known that Schwann cells are of neural crest origin. We hypothesise that glomus cells are of neural crest origin too. Neural crest stem cells (NCSC) can be isolated from mammalian fetal peripheral nerves.¹⁰ NCSC form three different cell types in culture, neurones, Schwann cells, and smooth muscle-like myofibroblasts.¹⁰ These myofibroblasts are positive for alpha-smooth muscle actin (SMA) and might be the precursors of the SMA positive glomus cells in the glomus organ of the nailbed. Therefore, it is possible that a second hit in the *NF1* gene in a SMA positive glomus cell results in a glomus tumour in NF1 patients in a similar way as a second hit in a Schwann cell is responsible for a neurofibroma. Further molecular work on these SMA positive cells is needed to substantiate this hypothesis. However, these glomus tumours are very small and it will be necessary to develop selective culture conditions to grow and expand these SMA positive tumoral cells as has been done for neurofibroma derived Schwann cells.¹¹⁻¹²

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