

# Case Resolution

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## DIAGNOSIS

Glomus tumor (synonyms: glomangioma, glomangiomyoma, angiomyoneuroma, neuromyoarterial aneurysm, vasculoneuroma).

## DISCUSSION

A glomus tumor is a benign and rare vascular tumor. It originates in the glomus body, which consists of a neuromyoarterial apparatus: it is composed of nerve cells, smooth muscle cells and vascular structures. It is located in the reticular layer, the deepest layer of the dermis, but it is distributed throughout the body, although it prevails in the hands and feet. Its structure consists of an afferent arteriole, a tortuous central arteriovenous anastomosis—also called the Sucquet-Hoyer canal, a collecting vein, an intraglomerular reticulum (containing glomus cells, unmyelinated nerve fibers and interstitial cells) and a capsule composed of a neurovascular reticulum. Glomus cells are specialized smooth muscle cells that derive from Zimmermann’s pericytes and are particularly dense around these dilated vascular spaces. In addition, there may also be increased nerve fibers and mast cells. It is, therefore, a highly specialized arteriovenous anastomosis. The glomus body is responsible for temperature regulation.

In 1812, Wood was the first to describe the clinical findings associated with the glomus tumor. The author reported cases of painful subcutaneous nodules presenting with pain and cold intolerance, but curable by excision. In 1878, Kolaczek described this type of lesion as a subungual tumor of the fingers. In 1924, Masson named the tumor, offering a complete description of it, as well as its pathological classification. According to Masson, the tumor originates in the neuromyoarterial glomus body, described by Popoff years later.

Histologically, a glomus tumor is a hamartoma resulting from hyperplasia of the neuromyoarterial glomus body components and typically comprises three parts (Figure 10). Depending on the predominant histological component, there are three different histological types of glomus tumors:

1. Myxoid or type I: also called glomangiomyoma, with predominance of the vascular component and smooth muscle cells. It is the rarest type (5%).

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2. Solid or type II: it is poorly vascularized and has few smooth muscle cells. It is the most common type (75%).
3. Vascular or type III: also called glomangioma. It is highly vascularized and accounts for 20% of all glomus tumors.

Regarding immunohistochemistry, these tumors are stained with vimentin and alpha smooth muscle actin, as well as CD34. They are positive for SMA, MSA, calponin, h-caldesmon and type IVM collagen, and negative for cytokeratin and S100. In hereditary cases, there is proven overexpression of the basic fibroblast growth factor (bFGF), a potential modulator of the disease activity and systemic involvement.

The cells lack markers for endothelial cells. The absence of desmin in tumoral cells is a feature shared with some vascular smooth muscle cells.

In solitary glomus tumors, multiple nerve fibers containing substance P, a sensory primary afferent neurotransmitter, mediator of the painful stimulus, have been identified.

Macroscopically, single tumors are usually small, between 1 and 5 mm in diameter (the one presented here measured 14 mm, although they can reach up to 30 mm), encapsulated, and their color varies between pink and dark blue/purple.

They can manifest as single or multiple tumors. Solitary tumors are more common and mainly located in the acral areas, and account for 1% to 5% of soft-tissue tumors of the hands. They are more common in women in the fourth decade of their life (from 30 to 50 years of age), although they have been described in all age ranges.

Although glomus tumors can occur in any part of the body, up to 75% occur in the hand and about 65% of these are located in the fingertips, particularly in the subungual space. Other sites may include the wrist, forearm and foot, but these tumors can develop anywhere in the body. In fact, they have been described in very uncommon sites, such as the patella, tendons, bones, eyelids, colon, rectum, kidneys and cervix.

When it comes to multiple glomuvenous malformations, they show an autosomal dominant pattern of inheritance, with almost exclusive transmission from father to son. In genetic studies, a mutation on chromosome 1p22.1, a gene encoding glomulin (GLMN), which function remains unknown, has been identified along with three related genes on the long arm of chromosome 11. The presence of multiple digital glomus tumors is rare and has been reported, in several occasions, in patients with neurofibromatosis type 1.

Multiple glomus tumors account for less than 10% of cases (some series report up to 25%). They are rarely located in the subungual region. Pathologically, they are not encapsulated, unlike single glomus tumors, and show larger vessels. They appear at an earlier age and are more common in men. They are not usually painful, as opposed to single tumors.

They are usually benign, with very rare malignant variants. Findings suggesting malignancy include large size, deep location, infiltrative growth, mitotic activity, nuclear pleomorphism and necrosis. Some reports mention metastatic disease and death resulting from it. Glomangiosarcomas are a rare malignant variant that can be metastatic.

Although they are rare and benign tumors, glomus tumors extremely disabling. While their symptoms are very typical and their diagnosis apparently simple, the time period between the onset of the symptoms and the diagnosis and treatment is surprisingly long. It has been reported that the history includes severe pain without evident etiology during an average of one to seven years. Clinically, the classic triad of this tumor consists of hypersensitivity to pressure (the simple rubbing of the nail can make the patient reject any semiological maneuver), severe paroxysmal pain (resistant to pain killers and, sometimes, spread to the thenar eminence or the palm) and cold intolerance. Not all the symptoms are always present, but pain is the most common one. Occasionally, it is more severe at night and may disappear when a tourniquet is applied to the hand proximal to the lesion, reflecting the vascular nature of the tumor and the subsequent effect of ischemia.

Visual examination reveals erythematous-violaceous or blue spots, depending on the depth of the lesion. The average size reported is 5 mm, and the largest tumors cause nail deformity and discoloration in one third of patients.

Elevation of the nail plate, distal onycholysis with increased Lovibond angle, and erythronychia have also been reported. Tumors growing on the nail seems to be determined by their location, and they can cause dystrophies when located below the nail matrix.

Medical history and physical examination are critical for the diagnosis. However, diagnosis is sometimes difficult, especially in early stages in which the lesion may be very small or when the signs are not florid, or the traditional triad is not fully manifested. When the clinical presentation is not the usual one, several clinical tests have been proposed:

1. **Love's pin test:** a pin or a sharp object is pressed against the nail plate. For this test to be positive, the patient must have severe pain with withdrawal reflex. Pain is not triggered if the test is applied in an area immediately adjacent to the painful spot. Test's sensitivity is 100%, but its specificity is 78%.

2. **Hildreth's sign:** it consists in causing a decrease in the blood flow to the affected region without producing ischemia. A tourniquet is made at the base of the finger, or the arm is extended upwards and a cuff is inflated up to 250 mmHg. With the resulting decrease in perfusion, the affected region is pressed: the pain must be reduced or disappear. When the tourniquet is released, the pain returns. The vascular nature of the tumor is probably the reason why the pain disappears. This test has a sensitivity of 77.4% to 92% and a specificity of 91% to 100%.

3. **Cold intolerance:** cold water or ethyl alcohol should be applied to the affected region to trigger the symptoms. The test is positive when the patient experiences severe pain. Its sensitivity and specificity are 100%.

4. **J test:** spontaneous pain radiating to the shoulder.

5. **Transillumination test:** performed in a dark room projecting light through the fingertip. An opaque red image is obtained from the area where the tumor is located and provides an estimate of its size. The sensitivity varies from 23% to 38%, and the specificity is 90%.

Imaging studies help confirm clinical suspicion and determine the location, characteristics and size of the tumor, which are useful for the surgical approach.

**X-rays:** In most cases, there are no pathological findings, although an increase in soft-tissue thickness can be observed, visualized as an increase in the distance between the bone and the nail. For this to be observed, the tumor must be large enough and longstanding. There is thinning or erosion of the cortical bone of the third phalanx. X-rays may show a well-defined osteolytic lesion with a sclerotic border in cases of rare intraosseous locations. It is good practice to take comparative X-rays on the healthy side.

**Ultrasound:** a non-invasive technique that can be used before surgery to detect the location, size and shape of tumors as small as 2 mm. In ultrasounds, the tumor appears as a well-defined highly-vascularized hypoechoic nodule. It can be used together with color Doppler ultrasound, which greatly increases its detection rate. The high-flow tumoral shunt makes this lesion appear hypervascular in color Doppler ultrasound, which is a specific finding useful for diagnosis. The limitation lies in the small, flat lesions and artifacts that the nail can create, as well as being an operator-dependent procedure.

**MRI:** it is the most useful imaging test for diagnosing the tumor, especially when there are no specific clinical signs. The lesions usually show a hyperintense signal in T2 (sometimes with a hypointense halo corresponding to the capsule), hypointense in T1 and with intense enhancement when IV gadolinium is used. MRI can be particularly useful for detecting early lesions, which are very small (even 2-mm lesions) and difficult to diagnose both on physical examination and other imaging tests, as well as in patients with recurrence or incomplete resolution of the symptoms after a previous surgery. In these cases, tumors are usually hypointense or isointense in T2, with little or no gadolinium enhancement and poorly defined margins due to the presence of postoperative scar tissue. Angio-MRI is a useful and complementary technique to conventional MRI to confirm the diagnosis. Typical angiographic findings are intense contrast uptake in the arterial phase and increased size in the late phase.

Differential diagnoses to be considered in these cases, especially due to their subungual location, include benign solid tumors (soft-tissue chondroma, keratoacanthoma, hemangioma, lobular capillary hemangioma), benign cystic lesions (mucoid and epidermal cysts) and malignant tumors (squamous-cell carcinoma and melanoma).

Pain, a symptom that most patients refer, leads to the inclusion, among differential diagnoses, of other painful tumors that can be located in the fingers (neuroma, eccrine spiradenoma, leiomyoma, ganglion or exostosis) or conditions such as type II complex regional pain syndrome, gouty arthritis or calcinosis.

The preferred treatment is complete surgical excision, including the tumor capsule. In most cases, pain relief occurs immediately after surgery. In other cases, recovery time can be two to four weeks, but the pain may take months to disappear. If the symptoms persist after three months or recur, tests should be repeated. Persistence may be due to incomplete excision or multiple lesions. Recurrence is unusual, but the reported risk is 1% to 18%, and it may be early if the excision was incomplete.

If the patient cannot or does not want to undergo surgery, indomethacin, as reported, can control the pain in 10 days. Other treatments are pulsed dye laser, argon laser and CO<sub>2</sub> or neodymium-doped yttrium aluminum garnet. Other treatment options include sclerotherapy with sodium tetradecyl sulfate, polidocanol, and hypertonic saline.

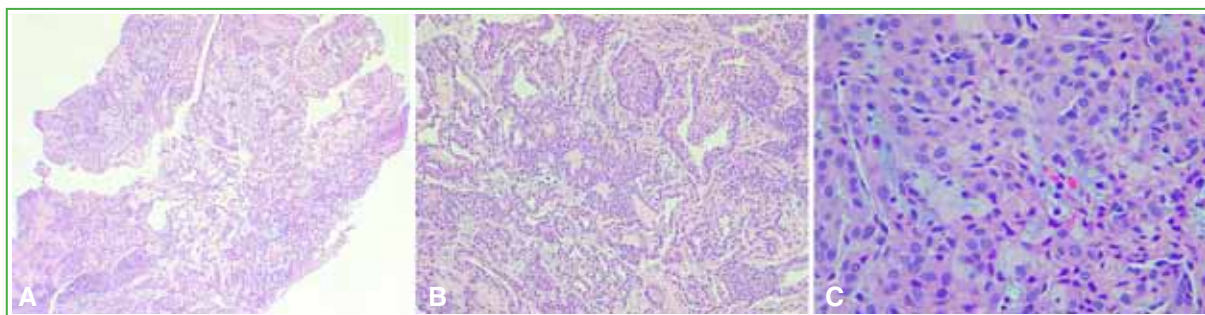
## CONCLUSIONS

Glomus tumors are benign rare vascular neoplasms, usually presenting as single lesions, that show a certain predominance in the acral regions (approximately 80% of the lesions are located in the upper extremities and most of them under the nail) resulting from hyperplasia of one or more parts of the glomus body. Patients can go years without being diagnosed, which could be explained, in part, by the small size and varied clinical presentation of these tumors, since they may not be palpable, or by the fact that physicians are not familiar with the classical symptoms and clinical tests. The clinical feature is the triad of cold intolerance, severe paroxysmal pain and precise localization of the pain. When there are typical symptoms, the precise diagnosis of the disease is facilitated by a physical examination and clinical tests.

Surgical removal is the current preferred treatment. Even when the lesion has been diagnosed clinically and by physical examination, it is important to locate the tumor preoperatively, as well as to have an idea of its size, since complete surgical excision is essential to avoid recurrence. For preoperative characterization, different imaging tests can be used, although MRI is the most useful, since it allows for determining the location and margins of glomus tumors, despite their small size, before excision, which helps correct surgical planning.

In addition to providing this information, MRI is useful for differential diagnosis of other lesions and to investigate the possibility of multiple tumors.

Recurrence after surgery is largely due to incomplete excision. In these cases, it is also recommended to order an MRI to rule out new or malignant lesions.



**Figure 10.** A. (x4), B. (x10), C. (x40). The histological sections show a nodular formation consisting of aggregates of glomus cells, with rounded nuclei and eosinophilic cytoplasm, organized around blood vessels immersed in a hyaline stroma with myxoid areas.

Conflict of interest: The author claims he does not have any conflict of interest.

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