_Glomus tumor of uncertain malignant potential in upper extremity: Case report and review of literature_

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**Abstract**

Malignant glomus tumors are a extremely rare soft tissue sarcomas, supposed originated from a benign glomus tumor. We report a case of glomus tumor of uncertain malignant potential occurring on the skin of volar area of arm of a 56-year-old woman.

We review the clinically features of the other similar cases that have previously been documented in the English literature and propose a guidelines treatment criteria.

**Keywords:** Malignant Tumors; Glomus Tumors; Sarcoma; Radiotherapy

**Introduction**

A glomus tumor is a benign neoplasm that derives from the glomus body, which is an anastomosis formed by an afferent arteriole and an anastomotic vessel called the Sucquet-Hoyer channel [1] and is surrounded by an efferent vein, nerve fibers and a capsule peripheral and has regulatory function of peripheral temperature.

The etiology is still unknown, through immunohistochemistry, its origin has been observed in vascular smooth muscle [3], it may be due to de novo mutations that affect the regulation of angiogenesis by activating a receptor specific for tyrosine kinase in the endothelial cell (TIE2) [3].

Most glomus tumors are usually solitary, small, normally less than 1 cm and red-violet. They can cause paroxysmal and lancinating pain due to changes in temperature and pressure.

Malignant glomus tumors are very rare, they can be locally aggressive and recur, they do not usually metastasize. The first case was described by Lumley and Stanfield as an atypical and infiltrating glomus tumor [1] Khoury et al.

It is thought that it can originate from a benign glomus tumor but this supposed transformation is not clear [3] In 1990 Gould et al. proposed the first classification scheme, based on analysis of six tumors: (1) locally infiltrative glomus tumor (LIGT a cytologically benign tumor with an infiltrative growth pattern and higher local recurrence rate), (2) glomangiosarcoma a true morphologically malignant arising in a benign Glomus Tumor(GABGT) and (3) de novo Glomangiosarcoma (GADN). None of the glomangiosarcomas in their series metastasized; however, the number of cases was small.

Folpe et al. reviewed 52 GTs with atypical morphological features and proposed a classification scheme based on 5-year cumulative metastatic risk: (1) malignant GT, which is associated with a metastatic rate of 38% and is defined as a tumor with size larger than 2 cm and with a deep location, or atypical mitotic figures, or moderate to high nuclear grade and with 5 or more mitoses/50 high power fields (HPFs); (2) GT of uncertain malignant potential, which has high mitotic activity and superficial location or large size only or deep location only; (3) symplastic glomus tumours, encompassing tumours with high nuclear grade in the absence of any other malignant features, probably reflecting a degenerative phenomenon; (4) glomangiomatosis, referring to tumours with histological features of angiomatosis coupled with an excess of glomus cells [6].

The last three categories did not show metastatic activity, which was restricted to the malignant GT subgroup only.

The latest edition of the World Health Organization (WHO) classification of tumors of soft tissue and bone indicates that the diagnosis of malignant GT should be made when a GT shows: marked nuclear atypia and any level of mitotic activity; or atypical mitoses [16].

These tumors seems to have an up to 40% metastatic rate. The term GT with ‘uncertain malignant potential’ is used for neoplasm not fulfilling criteria for malignancy but displaying at least one atypical morphological feature in addition to nuclear pleomorphism [7] Table 1.

### Table 1: Summary of clinical features (Folpe et al.) [15].

<table>
<thead>
<tr>
<th>Malignant Glomus Tumor</th>
<th>Glomus Tumor of uncertain Malignant potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Large size and deep location or 2) Atypical mitotic figures or 3) Marked atypia with mitotic activity</td>
<td>1) Superficial location with high mitotic activity or 2) Large size only or 3) Deep location only</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symplastic Glomus Tumor</th>
<th>Glomangiomatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Lacks criteria for malignant glomus tumore and 2) Marked nuclear atypia only</td>
<td>1) Lacks criteria for malignanglomus tumore or glo mus tumor of uncertain malignant potential and 2) Diffuse growth, resembling angiomatosis, with excess glomus cells</td>
</tr>
</tbody>
</table>

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**Clinical Case**

A 63-year-old woman referred in March 2016 by her Family Physician to the Dermatology Service for a reddish papular lesion with a 7-month history.

The patient has a reddish lesion on the right forearm since the beginning of summer 2015, which causes cramping and irradiated pain when touching the lesion. It has been growing gradually throughout this time and it has not bled.

In the initial physical examination, the lesion is described as reddish, vascularized, without erosions or ulceration, dome-shaped, on the right forearm. It measures 6 mm (Figure 1,2).

On the same day of the consultation, in Dermatology Unit, the lesion was removed.

The pathology result is a glomus tumor of uncertain malignant potential. The tumor has 6-9 mitosis per field. Knowing the result, patient is derived to our Musculoskeletal Tumor Unit (Figure 9).

A soft tissue MRI of the forearm is requested to rule out multifocal subclinical involvement and a TAC body. In MRI skin marking is performed in the area where the patient refers to the already excised lesion (lateral region of the forearm). Adjacent to the cutaneous and slightly anterior mark, a focal cutaneous thickening is identified that shows an increase in signal intensity in sequences with long TR and Gadolinium uptake of approximately 8 mm. It associates signal alteration and enhancement of the subcutaneous cellular tissue immediately underlying. In the recent surgical context, is not possible being able to rule out the presence of tumor residue locally. There no other lesions or presence of skin or subcutaneous pathological enhancement that suggests the presence of a multifocal affection.

After evaluating the case in the tumor committee, it was decided to carry out an enlargement of surgical margins, and then refer the patient to assess adjuvant Radiotherapy treatment. Simulation CT was performed in supine position using isocentric technique and arm support in custom mold. 0.5cm bolus was used. Between the days 06/15/16 and 07/26/16 by means of a linear electron accelerator, it is carried out. Radiotherapeutic treatment with 6Mv photons to the following volumes: PTV1: bed. The total dose administered was 63Gy and a fractionation of 210cGy / session. Doses to risk organs meet the criteria established by the Quantitative Analyses of Normal Tissue Effects in the Clinic tables. (QUANTEC) [33] (Figures 3 to 8).
### Table 2: Review of the cases of malignant glomus tumors of extremities including glomus tumor of uncertain malignant potential.

<table>
<thead>
<tr>
<th>AUTHOR, YEAR</th>
<th>LOCACIÓN, SIZE</th>
<th>DIAGNOSIS</th>
<th>ADYUVANT TREATMENT</th>
<th>RECURRENCE</th>
<th>METASTASIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gould et al. 1990</td>
<td>Hand, 2.8 cm</td>
<td>glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fernando et al. 1997</td>
<td>Thigh 0.8 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Noer et al. 1991</td>
<td>Knee 0.6 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Aiba et al. 1988</td>
<td>Scapula 0.5 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Folpe et al. 2001</td>
<td>Shoulder 5 cm, 8 Arms, 6 fingers, 1 Wrist</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>Yes (in the case of the shoulder)</td>
</tr>
<tr>
<td>Khoury et al. 2005</td>
<td>Hand 3 cm</td>
<td>Glomangiosarcoma</td>
<td>Radiotherapy and Chemotherapy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Park et al. 2003</td>
<td>Hand 4.5 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Watanabe et al 1995</td>
<td>Arm 1 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Wetherington et al 1997</td>
<td>Finger 0.5 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rishi et al 2012</td>
<td>Shoulder 0.9 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Perez de la Fuente et al 2005</td>
<td>Hand 0.5 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bolado et al 2017</td>
<td>Hand 5.2 cm</td>
<td>Glomangiosarcoma</td>
<td>Radiotherapy</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Woodward et al 2016</td>
<td>Hand 5 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Shinwer et al 2000</td>
<td>Scapula 1 cm</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kreutz et al 1987</td>
<td>Thigh n/d</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>Yes (to jaw)</td>
</tr>
<tr>
<td>Watanabe et al 1998</td>
<td>Hip n/d</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Baral et al 2011</td>
<td>Left Thumb, 6x2cm</td>
<td>Glomus tumor of uncertain malignant potential</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Binesh et al 2012</td>
<td>Scapula 2 cm</td>
<td>Glomus tumor of uncertain malignant potential</td>
<td>Chemotherapy</td>
<td>Yes</td>
<td>Yes, (to the lung)</td>
</tr>
<tr>
<td>Luzar et al 2018</td>
<td>Legs 6, Arms 4, Face 1</td>
<td>Glomangiosarcoma</td>
<td>No</td>
<td>Yes in one case</td>
<td>No</td>
</tr>
<tr>
<td>Present case</td>
<td>Forearm 0.6 cm</td>
<td>Glomus tumor of uncertain malignant potential</td>
<td>Radiotherapy</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Figure 1 & 2:** Initial papular lesion. Dermathoscopy.

**Figure 3:** Surgery design: enlargement of surgical margins.
Figure 4 & 5: Block excision, including fascia, muscle and vessel.

Table 6 & 7: Anatomopathological study piece.

Figure 8: Scar after radiotherapy.

Figure 9: Pathology findings: The lesion was located in the dermis, bulging the epidermis (photo 9-a) and had a maximum diameter of 0.5 cm. Histologically, it consisted of a homogeneous proliferation of cells of medium size, rounded or slightly fusiform, with central nuclei without evidence of atypia (photo 9-b). Necrotic areas were not observed. The mitotic index was moderately high, with a count of 6-9 mitoses per 10 high-power fields (photo 9-b, arrows). The immunohistochemical study showed positivity for vimentin and smooth muscle actin (remember that the glomocito cell is a modified muscle cell) (photo 9-c). It was negative for pancytokeratin (AE1-AE3) and CD34 (endothelial marker). The proliferation index, measured with immunostaining for ki67, was relatively high and, in zones, reached 30-35% (photo 9-d). All this was diagnosed as "glomus tumor of undetermined malignant potential (" borderline ") because it included only one of the criteria for malignancy (excluding cytological atypia, if any) and was a mitotic index greater than 5 × 50 fields of great increase, lacking others (size greater than 2 cm, deep location, subfascial, presence of atypical mitosis or infiltrative pattern) that would have definitively labeled it as malignant (glomangiosarcoma).

Discussion

Glomangiosarcoma is very rare. The first case was reported by Lumley and Stansfeld in 1972, who used the term of malignant glomus tumor to described a lesion located deep to the Achilles tendon in a 24-year-old female with severe and persistent right distal lower extremity pain that finally required an above-knee amputation [1]. The first case series of glomangiosarcoma was reported by Gould et al in 1990. Glomus Tumors (GTs) are uncommon, comprising 1.6% of 500 consecutive soft tissue tumors reported from the Mayo Clinic. The great part of GTs are small, benign tumors that occur in the dermis or subcutaneous tissue of the extremities. However, GTs may show unusual clinical features, such as large size, deep soft tissue or visceral location, infiltrative growth pattern or multicentricity became malignancy [10]. Over the years, the malignancy of GTs has been more of a concept than a reality. Although several histologically malignant GTs have been reported, biological confirmation of malignancy in these cases was lacking, probably because many were superficial and therefore cured by therapy. A second compounding factor was the fact that the rare malignant GTs that produced metastases lacked a benign glomus component, and hence the accuracy of the diagnosis was questioned. The first report of a clinically malignant (ie, metastatic) GT is that of Brathwaite ann Poppiti [6].
Aiba et al suggested using the term glomangiosarcoma when a sarcomatous component arises in the background of a pre-existing glomangioma [3]. Rodríguez-Justo et al reported a clinicopathological review of 19 cases of glomangiosarcoma and de novo glomangiosarcoma, including their case of glomangiosarcoma arising in benign glomus tumor [4], Kreutz et al reported the first metastatic glomangiosarcoma in 1987 in a 33-year-old male with a large lesion found superficially on the thigh with metastasis to maxilla [5]. Since then, a few more cases with metastasis have been reported and outcome in most of them was lethal [5-7].

The criteria for malignancy in GTs proposed by Folpe et al., has a main limitation, the fact that they do not reflect the true biological potential of GTs when occurring at sites different from deep soft tissues, such as visceral organs and skin. Furthermore, it has been argued that, due to the significantly smaller size of GTs presenting in the skin in comparison to their deep soft tissue and visceral counterparts, such malignancy criteria are also difficult if not impossible to apply.

The treatment for glomangiosarcoma is complete surgical excision. No radiation or chemotherapy is recommended at this time for primary, recurrent or metastatic disease, although their use had been reported by several authors [8,9].

A glomus tumor of uncertain malignant potential is defined as a glomus tumor with some, but not all, criteria for malignancy and without a known metastasis. The designation of a “uncertain malignant potential” was based on the high proliferative activity, the tumor size and location, and the lack of WHO malignancy criteria such as marked nuclear atypia, necrosis, or atypical mitoses [12].

Prognosis of glomus tumor of uncertain malignant potential is good but the number of cases is small and the follow up relatively short. Metastasizing GTs are rare and according to some reports, GTs of uncertain malignant potential did not metastasize [3]. However, it was not true about a case presented by Binesh et al in 2012 [27] of glomus tumor of uncertain malignant potential raised in scapula and characterized by a relatively large size 2cm and high mitotic activity, and lack of atypical mitotic figures, which recurred three months after surgery with bilateral pulmonary metastasis, they considered it as clinically malignant (metastasizing) atypical GT. Folpe reported that high nuclear grade, infiltrative growth and vascular space involvement were not associated with metastasis, however in Binesh case, vascular invasion was present, even in the initial specimen, which shows that vascular invasion is an ominous finding.

None of the clinicopathological parameters evaluated to date have shown to predict the disease outcome (e.g., local recurrence, development of metastatic spread) in cutaneous or superficial malignant GTs. Furthermore, the currently established malignancy criteria for cutaneous GTs can be difficult to apply mainly due to their smaller size. Likewise, counting mitotic activity per 50 HPFs can often not be accomplished in GTs occurring at superficial locations.

Luzar et al [11] suggest that cutaneous malignant GTs follow a more indolent clinical course than their deep soft tissue counterparts, probably reflecting their earlier detection at superficial sites and their smaller size on detection.

Although it has been described that this type of tumors of uncertain malignant potential, does not metastasize, there is a published case with early recurrence and pulmonary metastasis, so that in this case despite the small size of the lesion, because it was an unplanned surgery with marginal margins we decided to perform a margin expansion surgery with free margins and posterior adjuvant radiotherapy treatment. After three years of follow-up, the patient has not presented local recurrence or metastatic disease.

**Conclusion**

We believe that in Glomus tumor of uncertain malignant potential it is necessary to perform a surgery with wide margins and to propose adjuvant radiotherapy in case of narrow margins as well as a close and long term follow-up in the same way as if it were a glomangiosarcoma. In case of unplanned surgery is necessary perform a margin expansion surgery followed by adjuvant radiotherapy [34].

**References**


