

Low-Grade Malignancy Glomus Tumor in a Setting of Multiple Glomus Tumors – Case Report

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Abstract

Citation: Vasilevska-Nikodinovska V, Samardjiski M, Jovanovik R, Ilievski B, Janevska V. Low-Grade Malignancy Glomus Tumor in a Setting of Multiple Glomus Tumors – Case Report. Open Access Maced J Med Sci. 2019 Dec 15; 7(23):4082-4088. <https://doi.org/10.3889/oamjms.2019.610>

Keywords: Glomus tumor; Multiple localization; Low grade malignancy; Intramuscular; Kidney; Cardiac; Breast

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Received: 12-Jun-2019; **Revised:** 15-Aug-2019; **Accepted:** 16-Aug-2019; **Online first:** 10-Dec-2019

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

BACKGROUND: Glomus tumors are rare neoplasms accounting for less than 2% of all soft tissue tumors but multiple lesions may be seen in up to 10% of the patients. Solitary glomus tumor (GT) most frequently appears as small nodule in specific locations such as subungual region or deep dermis. However, rarely these entities have been observed in extracutaneous locations such as the gastrointestinal, cardiovascular, respiratory tracts, and other visceral organs. A small fraction of the GTs may present as tumors of uncertain malignant potential or as malignant glomus tumors.

CASE PRESENTATION: We report a patient with multiple glomus tumors on the time of diagnosis, which was histologically diagnosed as an atypical glomus tumor following resection of a tumor thrombus in the left renal vein, inferior vena cava thrombus with intracardial extension, and mitral valve specimen. The intramuscular lesion from the thigh was diagnosed as a glomus tumor of uncertain malignant potential. Further examinations revealed multiple lesions through her body: kidneys, breast, heart and subcutaneous tissue. The diagnosis of glomus tumor of uncertain malignant potential versus glomus tumor with low malignant potential could be quite challenging, and the clinical course may be as a determining factor for final diagnosis.

CONCLUSION: To our knowledge, this is the only known case of glomus tumor with multiple organ involvement and aggressive biological behavior at presentation.

Introduction

Glomus tumors (GTs) comprise less than 1,5-2% of soft tissue tumors, and less than 10% of them consist of multiple GTs (MGTs) [1], [2], [3]. Solitary GT most frequently appear as small nodules in specific locations such as the subungual regions of digits or the deep dermis of the palm, wrist, forearm, and foot. Rarely, these entities have been observed in extracutaneous locations, where the normal glomus body may be sparse or even absent, such as the gastrointestinal, cardiovascular, respiratory tracts, and other visceral organs [3].

Malignant Glomus Tumors (MGTs) may present as familial or sporadic. Familial MGTs show

autosomal dominant inheritance pattern, rarely associated with MEN II, A-V malformations or brachydactyly. In some cases, rearrangements of the glomulin gene (1p21-22) have been found [1].

A small fraction of the GTs may present as tumors of Uncertain Malignant Potential. Tumor size, mitotic activity and location, have been shown to be the major parameters correlating with the biological behavior of these tumors [4]. In such cases the clinical course of the disease cannot be readily anticipated, thus making the therapeutic approach difficult [2], [3], [4], [5], [6], [7], [8]. To our knowledge, this is the only known case of glomus tumor with multiple organ involvement and aggressive biological behavior at presentation.

Case Report

A 38-year-old woman contacted her physician after she noticed two weeks previously, a mass at the anterior aspect of the left thigh. On CT, the lesion was slightly hypodense and located within vastus lateralis muscle, without intralesional calcifications or signs for hemorrhage (Figure 1A). After contrast administration there was a mild inhomogeneous peripheral enhancement in the early arterial phase, followed by subtle homogenous enhancement of the entire lesion in the delayed phase (Figure 1B). Magnetic resonance imaging showed a well-circumscribed lobulated mass with the largest diameter of 6 cm (craniocaudal), isointense to muscle on T1-weighted image (WI), inhomogeneous high signal on T2WI and with presence of mild peritumoral edema. After Gadolinium (Gd) contrast administration, there was inhomogeneous enhancement of the lesion (Figure 1C, 1D, and 1E). Histopathological examination of the core biopsy specimen showed a small round cell tumor, in keeping with a sarcoma due to diffuse immunoreactivity with Vimentin, excluding Lymphoma, epithelial malignant neoplasm, but not excluding Ewing's sarcoma due to focal immunoreactivity with CD99 antibody. A suggestion for further cytogenetic examination was given (Figure 1F).

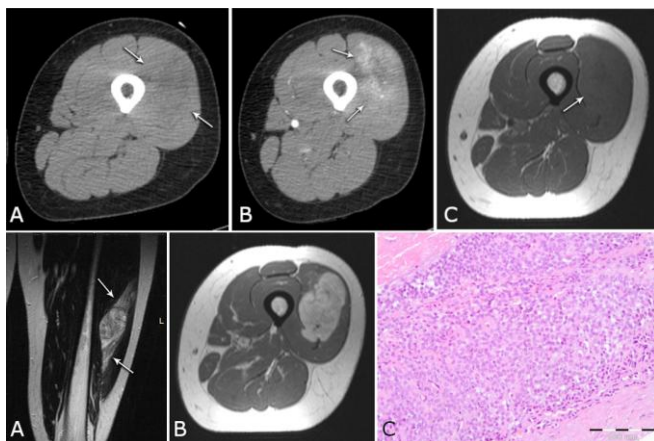


Figure 1: CT scan and Magnetic Resonance Imaging of the left thigh and corresponding histopathology of the core biopsy; A) pre contrast; B) after intravenous iodine contrast administration, early arterial phase; C) T1WI, axial plane; D) T2WI coronal plane; e) T1WI, axial plane, after intravenous gadolinium based contrast administration; F) Core biopsy specimen. The lesion is slightly hypodense compared to the normal muscle and is located within the left vastus lateralis muscle belly (arrows) A). On CT after contrast administration B) there is mild inhomogeneous peripheral enhancement of the lesion on early arterial phase (arrows), followed by subtle homogenous enhancement of the entire lesion in the delayed phase. On MR, within the left vastus lateralis muscle, there is a well-circumscribed lobulated mass, iso-intense to muscle on T1WI (arrow) C), and of heterogeneous signal on T2WI (arrow) D). The maximum craniocaudal diameter of the lesion is 6 cm. Note also mild peritumoral edema above upper and below lower pole of the lesion (arrows) D). After intravenous Gd administration, there was marked inhomogeneous enhancement of the lesion E). Core biopsy specimen shows highly cellular neoplastic tissue composed of relatively uniform, small to medium sized cells in diffuse-solid arrangement and foci of vaguely lobular architecture (HE x100) F)

Abdominal CT showed bilateral lesions of the kidneys, a 6 cm large lesion in the lower pole of the right kidney and 12 cm large lesion in the lower pole of the left kidney. Both lesions were isodense on the precontrast image, with enhancement of the central part of the lesions at the arterial phase followed by mild inhomogeneous enhancement in the delayed phase (Figure 2).

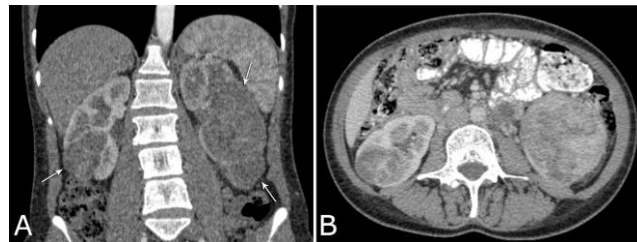


Figure 2: CT scan of bilateral kidney lesions, coronal reformatted A) and axial B) images. On abdominal CT scan after intravenous contrast administration there are large lesions within both kidneys, which are less enhancing than the surrounding cortex (arrows). On the distal pole of the right kidney 6 cm large lesion is present (craniocaudal diameter). The deformation of the contour of the left kidney (arrows) A) and distal pole enlargement of the left kidney due to 12 cm large lesion causing compression of the pyelocaliceal system. Both lesions are inhomogeneously isodense on the native scan, and show enhancement of the central parts at the arterial phase followed by mild inhomogeneous enhancement of the entire lesion in the delayed phase B). A thrombotic mass was present within the left renal vein extending within the inferior caval vein (not shown)

A thrombotic mass within the left renal vein and inferior caval vein extended within the right atrium. On chest CT scans after intravenous contrast administration lobulated isodense masses were seen in the left ventricle and anterior aspect of the mitral valve with thickened left wall of the left ventricle which enhanced inhomogeneously on venous phase (Figure 3).

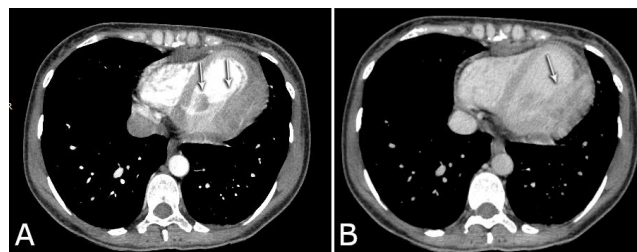


Figure 3: Cardiac glomus tumor presented on CT scan. On chest CT scans after intravenous contrast administration a lobulated isodense masses are seen in the left ventricle and anterior aspect of the mitral valve with thickened left wall of the left ventricle (arrows) A); On venous phase there is inhomogeneous mild enhancement of the lesion of the left ventricle wall (arrow) B)

An additional lesion was found in the left breast (Figure 4) and two lesions within the subcutaneous fat of anterior abdominal wall (diameter 1 cm each).

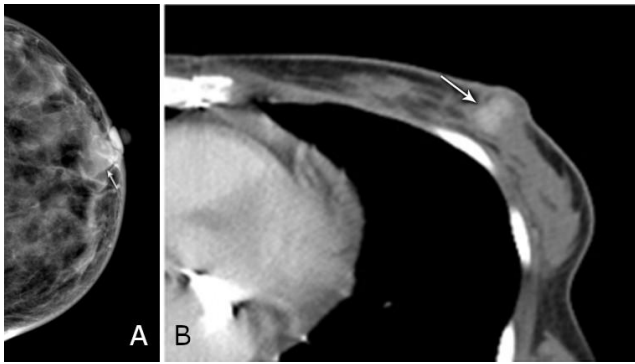


Figure 4: Imaging of glomus tumor on the left breast; A) Mammography; B) CT scan late venous phase. At mammography, craniocaudal view there is a retro-areolar dense lobulated lesion (arrow) A). On the chest CT scan after intravenous contrast material administration the lesion is highly vascular with homogenous enhancement on late venous phase B) presented as well-delineated lobulated lesion measuring 1,5 cm in diameter (arrow)

Further examination of the patient and therapy was done in another institution, where a core biopsy of the left kidney lesion suggested Ewing's sarcoma.

Urgent cardiac surgery was done, due to deterioration of cardiac symptoms (hypotension, dyspnea, shortness of breath, paroxysmal atrial fibrillation, decrease of ejection fraction under 30%) before any other therapeutic treatment. Preoperative cardiac ultrasound, which was six weeks after initial cardiac CT examination (Figure 3), showed a fibrillary mass within the left ventricle, with a diameter of 3.5 cm, located near the thickened anterior mitral valve. During systole the mass extends to the aortic valve. A mobile hyperechoic mass with similar ultrasound characteristic is seen in the right atrium, with a maximum length of 5 cm, extending within the right ventricle during diastole. Cardiac surgery was performed, with thrombectomy and mitral valve replacement and placement of inferior vena cava filter, in suprarenal position.

Shortly after the cardiac operation, the patient started with the first line chemotherapy according to VAC protocol (vincristine 1.5 mg/m², doxorubicin 75 mg/m², and cyclophosphamide 1200 mg/m² on day 1 [9]). Two cycles of chemotherapy has been administered until the histopathological diagnosis was revised as atypical glomus tumor, following histopathological examination of the cardiac resection specimen and vena cava thrombotic/tumoral masses. The Ewing's chemotherapy regime was discontinued and further chemotherapy with temozolomide 150 mg/m² (day 1-5) has been recommended.

Three months later the follow-up images of the thigh lesion showed enlargement of the lesion and occurrence of small intramuscular lesions with similar MR appearance located in the same and in opposite leg (Figure 5). The main thigh lesion and nearby satellite nodule was removed with free surgical margins.



Figure 5: Follow-up MR images on the thigh, after three months; A) Axial T1WI after intravenous contrast (Gd) administration; B) Coronal FS T1WI after intravenous contrast (Gd) administration. There is slight enlargement of the primary lesion and occurrence of new small intramuscular lesions in the same and in contralateral leg (arrows)

Only postoperative positron emission computed tomography (PET-CT) scan was done, and previously described lesions on kidneys and breast, which were present before and after operation of the thigh lesion, shows no metabolic activities.

Histopathologic and molecular features

First diagnostic procedure was done in Macedonia. The initial core biopsy of the large soft tissue lesion located within m. vastus lateralis, revealed highly cellular neoplastic tissue composed of relatively uniform, small to medium sized cells in diffuse arrangement and foci of vaguely lobular architecture. The immuno-phenotype was quite non-specific rendering a diagnosis of small cell sarcoma.

Second diagnostic procedure was done in Turkey. Core biopsy of the left kidney mass, was histologically interpreted as a malignant tumor in favor of Ewing's sarcoma. Although CD99 negative, approximately 40% of the tumor cells were positive for EWS RNA binding protein 1 (EWSR1) (22q12) rearrangement on Fluorescent in situ hybridization (FISH). Unfortunately, the results from other institution did not mention the translocation partner locus for the EWSR1 rearrangement.

Third diagnostic procedure was done in Turkey. The "trombotic" masses surgically removed from both heart ventricles and vena cava inferior, and mitral valve specimen showed similar histological features to the kidney biopsy specimen, it expressed Smooth Muscle Actin (SMA) and laminin, besides vimentin. The Ki-67 proliferative index was around 1%. Based on all previous clinical and histopathologic data, diagnosis of Atypical multiple glomus tumors was made for the first time in this case.

Fourth diagnostic procedure was done in Macedonia. The surgical specimen consisted of skin fragment measuring 7 x 0.5 x 0.1 cm, with subcutaneous fat (8 x 3.5 x 0.7 cm) underlying skeletal muscle fragment (10 x 10 x 4 cm) and fragment of fascia (8 x 2 x 0.1 cm). On serial sections, a white-yellowish poorly demarcated tumor nodule (7

x 5.5 x 4 cm) was found in the muscle. The central part of the tumor consisted of dilated blood vessels filled with partially clotted blood. Another nodular lesion with the same macroscopic appearance was found subcutaneously. On light microscopy the tumor had a predominantly lobular architecture, composed of small-to medium-sized cells with moderate amount of eosinophilic or pale cytoplasm and relatively uniform nuclei with inconspicuous nucleoli (Figure 6), dispersed in scant collagen IV positive stroma with increased vascularity and foci of hemorrhage (Figure 7D). The cells had perivascular arrangement in many areas. Only one regular mitotic figure per 50 HPF (high power fields) was detected. Marked nuclear atypia and atypical mitotic figures were not found.

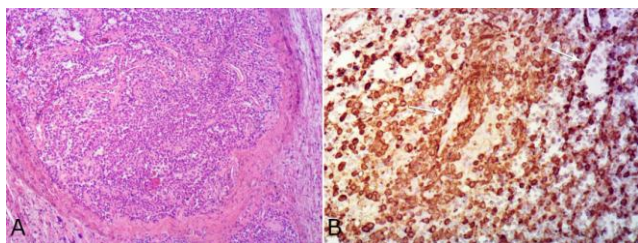


Figure 6: Histology of surgical specimen of the resected thigh mass. A lobular architecture of the tumor (HE x 40) (A); small irregular lumina are present within rich cellular lobules. SMA positivity (x 100) (arrows) (B)

The positive immunohistochemical findings were to the antibodies to smooth muscle activity (SMA), Vimentin, Caldesmon and Collagen IV, shown in Table 1. The Ki-67 was expressed in less than 5% of tumor cells, and only one mitotic figure per 50 hpf was detected (Figure 7A, 7B, 7C, 7D, 7E, and 7F). Tumor cells were negative for immunostaining against Desmin, S-100 protein, EMA, HMB45, CD31 and CD34. The diagnosis of glomus tumor of uncertain malignant potential was made due to histological features, tumor size and subfascial localization.

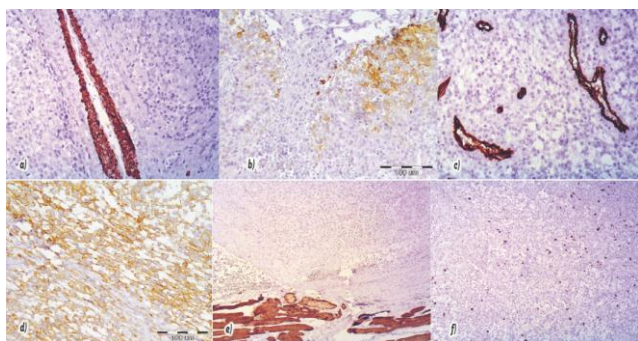


Figure 7: Microphotographs of various immunostaining (A); h-Caldesmon positive cells surrounding blood vessel (B); The same antibody labeling glomus cells in areas of solid growth; some of them lining small lumina (upper part of the microphoto) (C) CD34

Molecular analysis was performed using Next Generation Sequencing for 58 genes, Oncompass NGS hot spot panel, which did not identify any driver mutations. Polymorphisms and silent mutations were

detected in five genes (PDGFRA, RET, JAK1, PIK3R1, CHEK2), as well as KDR gene mutation (Q472H) in about 49% of the cells which was not considered a driver mutation. The tumor was FISH negative for HER2, FGFR1 and EGFR amplification/rearrangement. On these grounds, diagnosis of glomus tumor of uncertain malignant potential was proposed.

Follow up: The disease was stable 18 months after surgery of the thigh lesion and the start of Temozolomide (brand name Temodal) therapy, with absence of tumor progression.

Discussion

Glomus tumor is an uncommon mesenchymal neoplasm composed of modified smooth muscle cells, which are neoplastic counterparts of a perivascular glomus body. It is usually a small neoplasm that not exceeding 1 cm in diameter and located most commonly in the subungual region of the fingers in the distal extremities. It may also occur at the skin, subcutaneous fat and rarely in visceral organs [3], [4], [5], [6], [7], [8], [10], [11], [12], [13], [14], [15], [16].

GTs are more commonly seen in young adults [17] with rare onset after age 30 years.

A glomus tumor is typically painful triggered by cold, without improvement after analgetics [10], [15], [18], [19], [20]. The lesion is sensitive to pressure and touch [18], [19], [20]. The reported mean duration of symptoms is 7.2 to 14.6 years [15], [17]. Glomus tumors are solitary lesions in 82%-90% [15], [21]. Another studies reported as multifocal lesions in up to 25% of cases [17], [22]. Radiographic features of glomus tumors are usually not characteristic. On MRI, glomus tumors are of low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and enhance vividly on postcontrast images [15], [16], [18], [20], [23], [24], [25]. In cases of multiple glomus tumors each superficial nodule has a similar MRI presentation to a solitary glomus tumor [26]. A more lobulated shape of the lesion with a more heterogeneous enhancement pattern of the masses makes differentiation from malignant vascular or sarcomatous tumors difficult [15].

Multiple glomus tumor usually present with atypical clinical features, pathology and location [27]. There is usually no family history [26], which is the main reason for delay in diagnosis.

In our case, glomus tumors were histologically confirmed in the muscular compartment, kidney and heart. Imaging techniques showed similar to identical lesions in breast, most likely the same entity.

Visceral localization of glomus tumor is rare [8], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37],

[38], [39], [40], [41], [42]. To the best of our knowledge- synchronous location in multiple organs, as in our case, has not been reported.

Glomus tumor should be considered malignant when the tumor is larger than 2 cm, has deep subfascial or visceral location and has histologic features of malignancy, such as atypical mitotic figures or marked nuclear atypia and any level of mitotic activity [4].

Malignant glomus tumor may metastasize to the bone, brain, liver, lung, small intestine, or adjacent lymph nodes [4].

Glomus tumors not fulfilling the criteria of malignancy but have at least one atypical feature other than nuclear pleomorphism are labeled "Glomus tumor of uncertain malignant potential" [43], [44], [45]. In our case the thigh lesion was larger than 2 cm, and had subfascial localization but it had no histologic features of malignancy.

Malignant glomus tumors are very rare. Less than 10% of GTs are cases of MGTs. Most of the MGTs are sporadic cases, but occasionally may appear as familial cases with usually autosomal dominant inheritance pattern, may be rarely associated with MEN II syndrome, A-V malformations or brachydactyly [1], [4]. In some cases rearrangements of the glomulin gene (1p21-22) have been documented. Malignant glomus tumor present aggressive clinical behavior and specific immunohistochemical features. These tumors must be distinguished from several other types of malignancies, primarily EWS/PNET, hemangiopericytoma, epithelioid leiomyosarcoma and rhabdomyosarcoma. In most cases the differential diagnosis is relatively straightforward, based on morphology and specific immunophenotype, although in minority of cases it may be challenging. Unlike EWS/PNET, GTs are CD99 negative.

Solitary fibrous tumor shows a mixture of spindle and epithelioid cells with indistinct cell borders, usually staghorn tumor vessels, generally more hazard architecture, and show less frequently SMA expression. Epithelioid leiomyosarcoma shows more diffuse architecture and are less vascular, frequently contain areas of tumor cell necrosis, and more prominent mitotic activity. Rhabdomyosarcoma and variants with similar architecture and cellular composition to GTs, could be readily distinguished by desmin expression.

Our patient presented with multiple lesions at the time of diagnosis. The two consecutive surgeries, of the heart and of the thigh, revealed histology consistent with atypical glomus tumor and glomus tumor of uncertain malignant potential respectively. Histological criteria for malignant glomus tumor were not present.

Synchronous occurrence of glomus tumor in kidneys, heart and thigh, histologically confirmed and

the presence of similar lesions in other tissues and organs strongly suggest malignancy. Indeed the lesion in the left kidney was the largest one and was out of proportion in size to practically all other lesions. Both elements strongly suggest primary lesion in the kidney. The thigh lesion showed a satellite nodule near the first detected at second examination of the lesion, which indicates disease progression. Taking into consideration the above mentioned facts, the multiplicity, the disease progression and the criteria for malignancy of GTs [4], our case is considered as a malignant GT. This is also favored by the presence of multiple newly formed lesions, which would be interpreted as metastases in this context, and not multiple GTs. Another fact supporting this thesis is the presence of a lesion at the left heart ventricle wall.

On the other hand, the "benign" microscopic appearance contradicts the malignant nature of the tumor. The main diagnostic problem at initial diagnosis of such cases would be the absence of data about the clinical and biological behavior of the disease. In this regard, glomus tumor of uncertain malignant potential would be a more appropriate diagnosis, which would probably justify a wait and watch follow-up policy. Beside the serial sections made of the tissue samples taken from the thigh lesion there is always a possibility of not enough sampling in such cases when a divergence between the histology and clinical course appear.

Clinical condition controlled with Temozolomide stayed stable for 18 months; that also support the idea that the lesions we were dealing was most likely a neoplasm with low malignant potential.

That is why in our case, based upon clinical, histopathologic and molecular features of the tumor, diagnosis of glomus tumor of uncertain malignant potential versus glomus tumor with low-grade malignancy was outweighed. The rationale for favoring the diagnosis of GT with low malignant potential was the progressive clinical course, appearance of additional satellite nodules and the obvious need for chemotherapy, which finally resulted with the disease entering a steady state, with no remission, but neither further progression.

The variable immunophenotype of the different tumor samples, combined with the inconsistent molecular features and failure to detect common driver mutation in obtained samples could indicate the presence of biologically distinct multiple GTs, one (or some) of which had developed malignant features.

The management of glomus tumor remains controversial. Surgical resection is primary treatment option for tumors in suitable localization. Embolotherapy is not curative and the role of radiotherapy is controversial. Somatostatin was used in treatment of glomus tumor also, it provided slower growth, but was not curative [46], [47], [48], [49].

Our patient started chemotherapy for Ewing's sarcoma after kidney core biopsy showed 40% of the tumor cells positive for EWS RNA binding protein 1 (EWSR1) (22q12) rearrangement on Fluorescent in situ hybridization (FISH). This therapy was stopped, after two cycles, when the diagnosis of atypical glomus tumor was made on the basis of histological analysis of the thrombotic mass specimens from vena cava and specimen from mitral valve.

Due to progress of disease of our patient has started treatment with temozolomide as one of the chemotherapeutic options for salvage treatment of patients with unresectable or metastatic soft tissue sarcoma. Temozolomide is considered to be active agent in soft tissue sarcoma as monotherapy or in combination with other chemotherapeutic agents [49], [50].

Temozolomide as an oral agent and is performing as a prodrug of the alkylating agent dacarbazine. Therapeutic advantage of temozolomide is determined by its capability to alkylate/methylate DNA, which most often occurs at the N-7 or O-6 positions of guanine residues. This methylation damages the DNA and triggers the death of tumor cells [51], [52].

We conclude that diagnosis of glomus tumor of uncertain malignant potential versus GT with low malignant potential could be quite challenging, and the clinical course may be crucial for final diagnosis.

Despite absence of histological criteria for malignant glomus tumor, setting of multiple glomus tumors, disease progression and aggressive biological behavior at presentation indicated low grade malignant glomus tumor.

Compliance with Ethical Standards

Informed consent was obtained from the patient included in the study

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