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*Romanian Journal of Orthopaedic Surgery and Traumatology, Volume 4, Issue 1, January-June 2021. pp:3-8*
**doi:10.2478/rojost-2021-0002**

**Accepted: July 9th 2021**

**CASE REPORT**

# Malignant granular cell tumor of the arm – case report

**Mihai Mehedințu*, Răzvan Danciu*, Anca I. Toma*, Corina Ștefan*, Cristian R. Jecan****
*Department of Plastic and Reconstructive Surgery, „Prof. Dr. Agrippa Ionescu" Emergency Clinical Hospital, Bucharest, Romania
**Department of Plastic and Reconstructive Surgery, „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

**Correspondence to:** Mihai Mehedințu,
Department of Plastic and Reconstructive Surgery,
„Professor Dr. Agrippa Ionescu" Emergency Clinical Hospital, Bucharest,
7 Arh. Ion Mincu Street, District 1, Bucharest, Romania,
Mobile phone: 004 0723 556 905, E-mail: drmehedintu@gmail.com

## Abstract

Granular cell tumor (GCT) is a rare form of soft tissue cancer that is usually benign. Its malignant evolution is encountered in less than 2% of cases, having a more rapid and unfavorable evolution. Clinical presentation betraying malignant features could be increased tumor size, rapid growth, deep localization, and female gender.

This paper presents the case of a 52-year-old patient with a hard, rapidly evolving tumor in the left arm. The diagnosis of granular cell tumor was made based on histopathological examination using the Fanburg and Smith criteria to differentiate the formation as malignant, but with certainty this was subsequently confirmed by the existence of a metastasis. Surgical excision was performed and the evolution was favorable.

Evolution and treatment differ depending on the benign or malignant form, but surgical treatment with wide local excision is recommended. This may be followed by chemotherapy or radiotherapy, and follow-up of patients for the rest of their lives is mandatory.

Keywords: granular cell tumor, fine-needle aspiration biopsy, biceps brachii muscle, lymphatic tumoral invasion, soft tissue tumors, rhabdomyosarcoma

## Introduction

Granular cell tumor (GCT) is a rare form of cancer, whose origin has long been studied [1]. In 1926, Abriskossoff first described this tumor as a myoblastoma, originating from smooth muscles [2]. The neural origin was proposed in 1935 by Feyrter and confirmed in 1948 by Frust and Custer, thus calling granular cell neurofibroma. In 1962, the origin of Schwann cells was proved after performing immunohistochemistry and ultrastructure studies [3].

GCT is a rare tumor, most commonly benign (98%), which grows slowly in the subcutaneous tissues, more often in the head and neck, but can occur anywhere on the body, being a small, hard formation, with infiltrated edges [4-6].

These formations are more common among women than men, especially in the fourth and fifth decades of life, being very rare

in the pediatric population [7,8]. There has also been an increased prevalence of multiple forms in the African population [9].

Malignant giant cell tumors represent less than 2% of the total GCT, being more common in the extremities and having a faster evolution. They can ulcerate the skin and reach larger sizes (up to 15 cm). But, the most important thing is that they can metastasize; in contrast, the benign formations do not metastasize, but invade local lymph nodes [5,9].

The diagnosis is made by histopathological examination, characteristically having an increased amount of dense cytoplasmic lysosomes in different stages of fragmentation, determining the microscopic granular appearance [1].

## Case presentation

A 52-year-old male presented to the Plastic and Reconstructive Surgery Department complaining of a 5 cm firm nodular subcutaneous tumor that had evolved over a period of 6 months.

An ultrasound examination was performed at the level of the left arm, in its upper part, the internal portion, a hypoechoic, solid expansive formation, with polycyclic contour, of approximately 20/32 mm, was found. The formation developed at the level of the subcutaneous adipose tissue and encountered the deep muscular plane, from which it seemed well delimited.

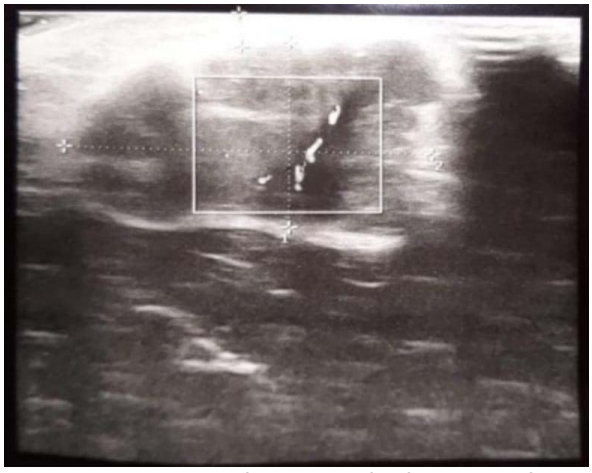

*Fig. 1 Solid expansive formation of soft tissue - left arm*

The histopathological diagnostic was made based on a fine-needle ultrasound guided aspiration biopsy revealing granular cell tumor with uncertain biological potential.

Upon CT examination of the head, neck and the thorax, small latero-cervical lymph node images with non-specific appearance were detected, without pulmonary parenchymal nodular lesions and signs of maxillary sinusitis.

Surgery was performed and the formation was excised. Intraoperatively, the adhesion of the formation to the biceps brachii muscle was identified. On histopathological examination, a tumoral proliferation was observed, with large, polygonal, fusiform cells, and granular cytoplasm, including the presence of large, homogeneous eosinophilic granules, with peripheral halo; nucleus located centrally with prominent nucleoli, aspect of nuclear pleomorphism, significant mitotic activity (with 7 mitoses per high-power field), and atypical mitoses. No necrosis was observed, the stroma presenting sclerosis focally. The tumor was imprecisely unencapsulated, impressively delimited, it had an infiltrative character with extension in the fatty tissue, fascia, and muscular tissue. Lymphatic tumoral invasion was observed, with unoccupied adjacent venule and arteriole.

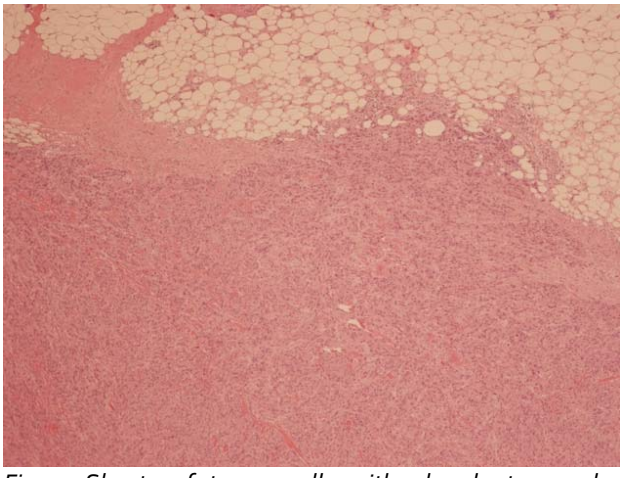

*Fig. 2 Sheets of tumor cells with abundant granular eosinophilic cytoplasm infiltrating into adipose tissue (hematoxylin and eosin; × 40 magnification)*

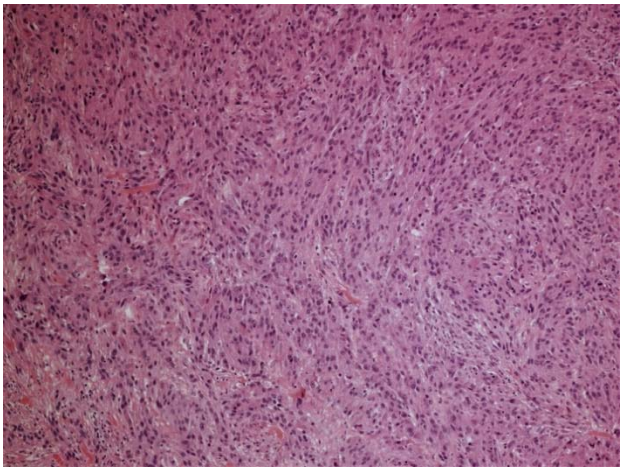

*Fig. 3 Epithelioid to spindle cells show nuclear atypia with large nucleoli and mitotic activity, features indicating malignancy [10] (hematoxylin and eosin; × 100 magnification)*

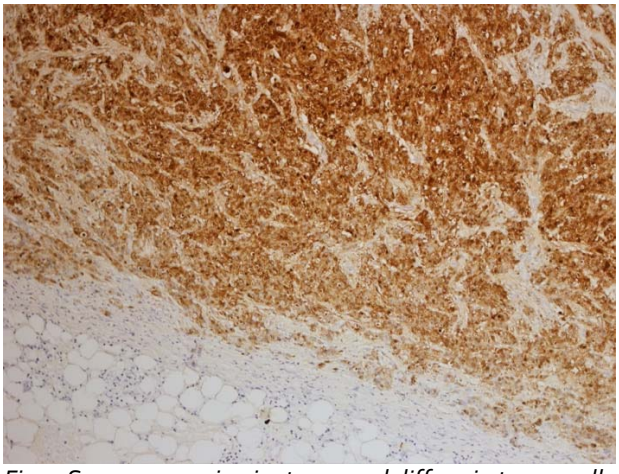

*Fig. 4 S-100 expression is strong and diffuse in tumor cells, helping to distinguish it from most entities in its differential diagnosis [11] (S-100 immunohistochemistry, x 100 magnification)*

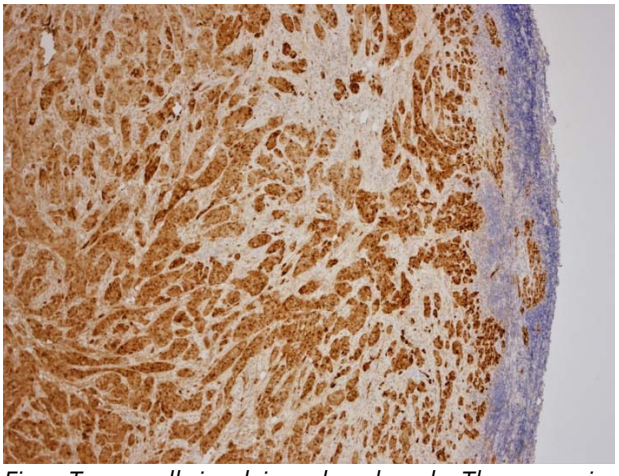

*Fig. 5 Tumor cells involving a lymph node. The expression of calretinin, a primarily neuronal protein, supports its neural differentiation [12] (Calretinin immunohistochemistry, x 40 magnification)*

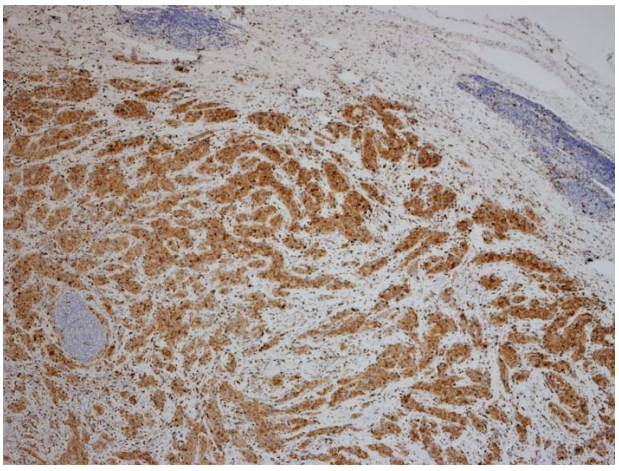

*Fig. 6 Tumor cells involving a lymph node. CD68 expression is variably positive and in a granular pattern, reflecting the accumulation of lysosomes in the cytoplasm [11] (CD68 immunohistochemistry, x 40 magnification)*

Immunohistochemistry was positive for S100, CD68, Calretinin, Melan A, and negative for HMB45, CD34, SMA, Desmin, and GFAP.

However, the lower edges of the specimen were invaded by the tumor, so it was surgically reoperated, with complete excision (safety margins of 2 cm), confirmed by a subsequent histopathological test. Compared to the previous aspect, the current recurrence retained its atypical histological character.

After 6 months, surgery was performed again for the excision of three lymph nodes, these being confirmed as metastases of malignant granular cells cancer (immunohistochemistry was positive for S100, Calretinin and CD68).

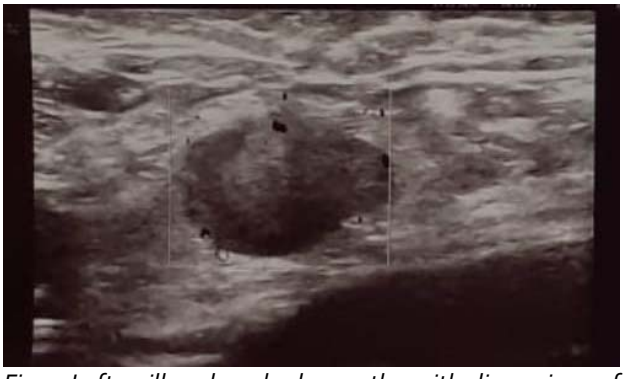

*Fig. 7 Left axillary lymphadenopathy with dimensions of 13/ 20.5 mm*

## Discussion

Granular cell tumors are a rare entity, representing only 0.5% of all soft tissue tumors [**13**]. Of these, however, only a smaller percentage of 1-2% are malignant tumors, with a 40% mortality rate [**14**]. Knowing this low incidence, clinicians need to pay special attention to the features of the formation in order not to miss this diagnosis and thus delay their surgical treatment.

Clinical features that predict malignancy include increased tumor size (> 5 cm), female gender, older age, round shape, deep location in tissue, rapid growth in a short period of time and the occurrence of local recurrences or distant metastasis [**15**].

For malignant granular tumors, the Fanburg-Smith analysis reports a local recurrence rate of 32% and a distant metastasis rate of 50%, which are considered negative prognostic factors along with increased tumor size, older age, increased mitotic activity and Ki-67 values greater than 10% [**16,17**]. Lymphatic or distant metastases occur between 3 and 37 months from the time of initial diagnosis and are, most often, located in the lungs, bones, and liver. For these considerations, the hypothesis of excising the sentinel node during the primary excision of the formation is proposed [**18**].

The non-specificity of clinical and paraclinical symptoms determines the making of a differential diagnosis with other types of tumors, such as rhabdomyosarcoma, alveolar soft part sarcoma, renal cell carcinoma, melanoma or paraganglioma. The diagnosis of certainty is made by histopathological and immunohistochemical examination [**18,19**].

Histopathological examination can accurately specify the morphological type of formation, but in the literature as well as in the case presented in this article, the criteria differentiating benign from malignant forms are difficult to achieve and the malignant form remains a controversial topic. Microscopically, the tumor cells appear large and polygonal in shape, with vesicular nuclei and cytoplasm with multiple eosinophilic granules, from which this tumor inherits its name [**20**].

Some morphological changes have been proposed as indicators of aggressiveness of GGT. Whereas Jardines [**19**] proposes the following changes that predict a diagnosis of malignancy: presence of necrosis, intense mitotic activity (> 2 mitoses per 10 high-power fields), vesicular nuclei showing nucleoli and spindle cells. Fanburg-Smith [**16**] adds two more observations: increased cytoplasmic nuclear ratio and pleomorphism. Analyzing these criteria, we observed that in our case, 5 of the 6 proposed criteria were fulfilled (except necrosis), which favored the diagnosis of malignancy of the formation.

Immunohistochemical examination is very important, complementing and supporting the histopathological examination. It confirms the neuronal origin by being strongly positive for S-100, neuron-specific enolase and calretinin [**16**]. The tumor is also positive for vimentin and the monoclonal antibody CD68, which recognizes 110-kDa lysosomal proteins [**21**]. All these immunohistochemical results from literature correlate with the results of the case presented by us.

The current treatment remains total surgical resection as radiotherapy and chemotherapy still showed inconclusive results [**22**]. However, complete excision with free margins is difficult due to the infiltrative nature of this disease, and due to the increased risk of recurrence or local lymphatic extension, re-intervention being often considered likely to be necessary. Wide excision is preferable, but in order to limit the excision of healthy tissue, the Mohs surgery technique has been proposed and successfully performed [**23,24**].

The patient should be closely monitored for the rest of his life both to prevent

recurrence and to monitor the progress of new adjuvant therapies.

## Conclusion

The particularity of the presented case resided precisely in the common clinical form of presentation, which drew the attention of doctors to the importance of differential diagnosis when talking about such a rare condition.

Since the treatment and evolution of GCT is different in benign and malignant forms, features such as rapid growth, clinical invasiveness and older age should raise the suspicion of malignancy.

Histopathological examination using the Fanburg-Smith criteria allows the disease to be classified as malignant, thus requiring wide excision. Although the excision margins are unclear and the role of primary sentinel lymph node excision is still debated, surgical treatment remains the best therapeutic solution, followed by adjuvant therapy. Regardless of the nature of the initial disease, all patients should be carefully monitored for the rest of their lives for the possibility of recurrence or distant metastasis.

**Conflict of Interest statement**

Authors state no conflict of interest.

**Informed Consent and Human and Animal Rights statement**

Informed consent has been obtained from all individuals included in this study.

**Authorization for the use of human subjects**

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies, is in accordance with the tenets of the Helsinki Declaration and was approved by the review board of „Professor Dr. Agrippa Ionescu" Emergency Clinical Hospital, Bucharest, Romania.

**Acknowledgements**

None.

**Sources of Funding**

None.

**Disclosures**

None.

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