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Case Report

A Rare Case of a Metastatic Malignant Abrikossoff Tumor

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Abstract
Abrikossoff tumor, also called granular cell tumor (GCT), is a neoplasm of the soft tissues which is most commonly a solitary, painless, and benign tumor. However, 2% of Abrikossoff tumors can be malignant. We report here the case of a 75-year-old male who presented a local recurrence of Abrikossoff tumor of the left thigh. The anatomopathological analysis concluded to a malignant GCT, and the F-18 fluorodeoxyglucose positron emission tomography showed multiple lesions in the lymph nodes and bones. The potential conversion to malignancy should alert practitioners because of the extremely poor prognosis. The diagnosis of malignant granular cell tumor should be based on a bundle of clinical and histological features and not solely on histologic features because of the challenging distinction between malignant and benign tumors due to the lack of well-defined criteria for the diagnosis of malignancy. Large size and recurrence are the most important clinical features predicting malignant behavior. Patients with a history of Abrikossoff tumor should be followed closely to monitor recurrence and malignant transformation. The apparent originality of our observation – which could lie in the evolution of a GCT tumor, initially considered as benign, to a malignant form – has to be challenged regarding the issue of classifying some cases according to the classical "benign" and "malignant" dichotomy.

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Introduction

Abrikossoff tumor, commonly called granular cell tumor (GCT), was described for the first time in 1926, by the Russian pathologist Alexei Ivanovich Abrikossoff [1], in a patient with a tongue tumor. It is classically described as more frequent in women between the 4th and the 6th decade, with a predominance in African Americans [2, 3].

The GCT can affect all parts of the body. The head and neck areas seem to be the most involved (45%–65%), especially the oral cavity [4]. This tumor is also found in the skin, gastrointestinal tract, respiratory tract, nervous system, and male and female reproductive system [5].

The origin of Abrikossoff tumor has been disputed for a long time. Since 1926, when a myogenic origin was proposed by Abrikossoff [1] who classified it as granular cell myoblastoma, due to the histological similarity with skeletal muscle fibers, several theories about the origin of GCT have been proposed, from striated muscle to histiocytes, fibroblasts, myoepithelium, and neural origins [5]. Currently, the neural origin, in particular from the Schwann cell type, is the most accepted theory, which is supported by the positivity of S100 protein and neuron specific enolase observed in immunohistochemical stains [4].

GCT is relatively rare, with a reported prevalence between 0.02% and 0.03% of all neoplasia [5], which explains the scarcity of the literature regarding this tumor. It is almost always benign (85–90%) [6] and is generally in a solitary, small, and painless form [2]. However, multiple, synchronous and metachronous forms have been described in up to 25% of cases in some series [7]. The malignant GCT (mGCT) form is an extremely rare entity, representing approximately 2% of all GCT. The diagnosis of mGCT is often difficult and controversial due to the deficiency of well-defined criteria for the diagnosis of malignancy.

Case Report

A 77-year-old Caucasian male was admitted to the geriatric unit for weight loss and asthenia for 2 years. His medical history included diabetes mellitus and atrial fibrillation. Physical examination revealed a voluminous (8 × 7 cm), painless nodular swelling of hard consistency, located in the medial part of the root of the left thigh (Fig. 1). We observed also 2 hyperpigmented cutaneous lesions in the back. There were no palpable lymph nodes or organomegaly.

The patient had noticed the left thigh's mass for 2 years, which gradually increased in size. He informed us that he had undergone, 5 years ago, an excision of a similar lesion, also located in the root of the left thigh. This lesion was an ulcerated exophytic nodule of 8 × 5.5 × 3.5 cm, with an ulcer measuring 4 cm. The microscopic examination showed a tumor process composed of cells grouped in small clusters with rounded to oval nuclei and eosinophilic cytoplasm with fine granules. The resection margins were clear. Immunohistochemical (IHC) stains were positive for CD68, S100, and CD163. The pathologist concluded to a benign Abrikossoff tumor. A liver echography and thoraco-abdominal computed tomography (CT) were also performed after the tumor resection and did not reveal any other lesion.

Laboratory investigations were within normal limits, except a moderate anemia and elevated C-reactive protein at 50 mg/dL. Autoimmune and infectious serologies were negative. Immunophenotyping on the peripheral blood sample did not show any argument for lymphoma.

We proceeded to a total resection of the left thigh mass and a biopsy for the cutaneous lesions of the back. The surgical specimen of the left thigh showed a poorly delimited, multilobulated, whitish to greyish, indurated mass, measuring 6 × 6 × 5 cm at excision (Fig. 2). The microscopic examination revealed a poorly defined mass, consisting of ribbons/nests of large

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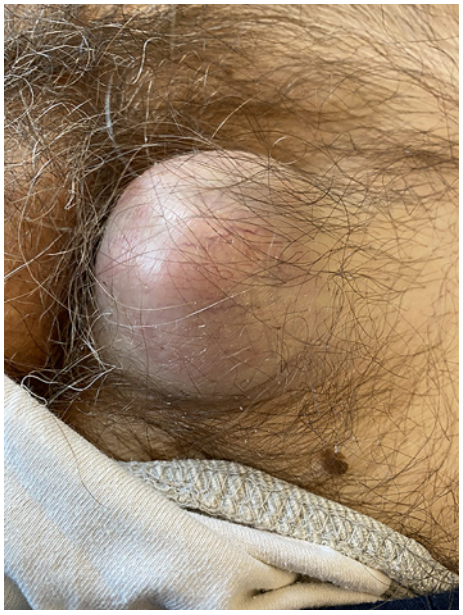

Fig. 1. Voluminous nodular swelling located in the medial part of the root of the left thigh, corresponding to a recurrent granular cell tumor.

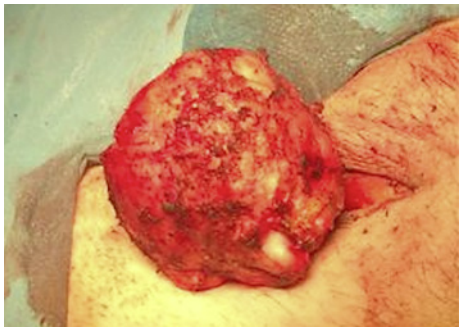

Fig. 2. Excision of the left thigh's mass, measuring 6 × 6 × 6 cm.

polygonal or spindle cells, containing an abundant eosinophilic cytoplasm (PAS coloration+) with coarse granules and rounded to oval central nucleus, nuclear pleomorphism, and macronucleolus. No necrosis was observed, and 2 mitotic figures were seen per 10 high-power fields (2/10 HPF). The tumor cells were separated by thin collagenous bands, and no evidence of metastatic infiltration of lymph nodes was found (Fig. 3). IHC staining was positive for inhibin, S100, and CD68. Contrariwise, there was no expression of anti-MelanA, anti-Pancytokeratine, anti-AE1/AE3, and anti-CLA immunohistochemistries. The Ki-67 index was low. Therefore, the diagnosis of a recurrent GCT was made.

The anatomopathological study of the back skin lesions revealed a melanoma in situ for 1 lesion, while the second lesion was a spreading superficial melanoma, with a Breslow depth of 0.10 mm and a Clark level II. No BRAF-V600 mutation was detected.

F-18 fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) was performed and showed hypermetabolic area in the left inguinal region with a standardized uptake value (SUV) of 7.7, associated with hypermetabolic lesions disseminated throughout the axial and peripheral skeleton and supra- and infradiaphragmatic lymph nodes (SUV 15.6) (Fig. 4). Finally, we performed a CT-guided bone biopsy of the right iliac crest, which was the most accessible hypermetabolic lesion in FDG-PET/CT, but it was not conclusive.

Based on these findings, we concluded to the diagnosis of metastatic mGCT. Unfortunately, due to a significant deterioration of the patient's general condition, no other examination

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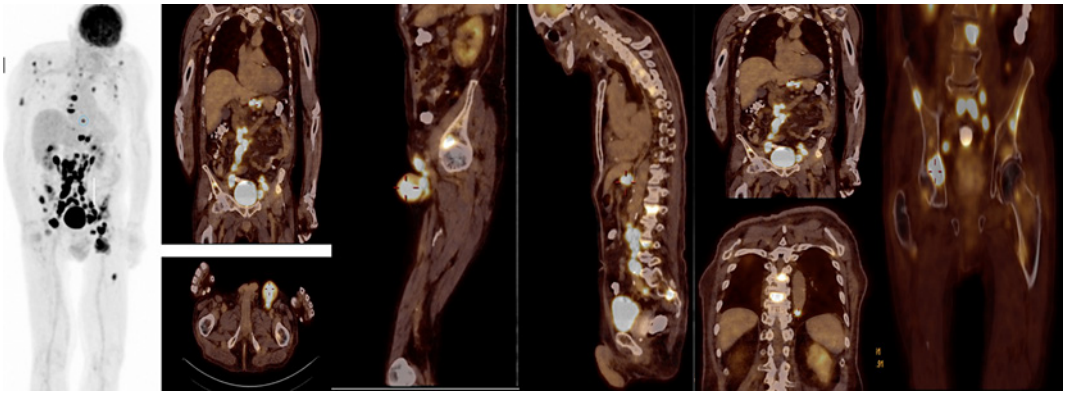

Fig. 3. F-18 fluorodeoxyglucose positron emission tomography/CT showing increasing FDG uptake area in the left inguinal region (SUV = 7.7), the axial and peripheral skeleton, and supra- and infradiaphragmatic lymph nodes (SUV = 15.6).

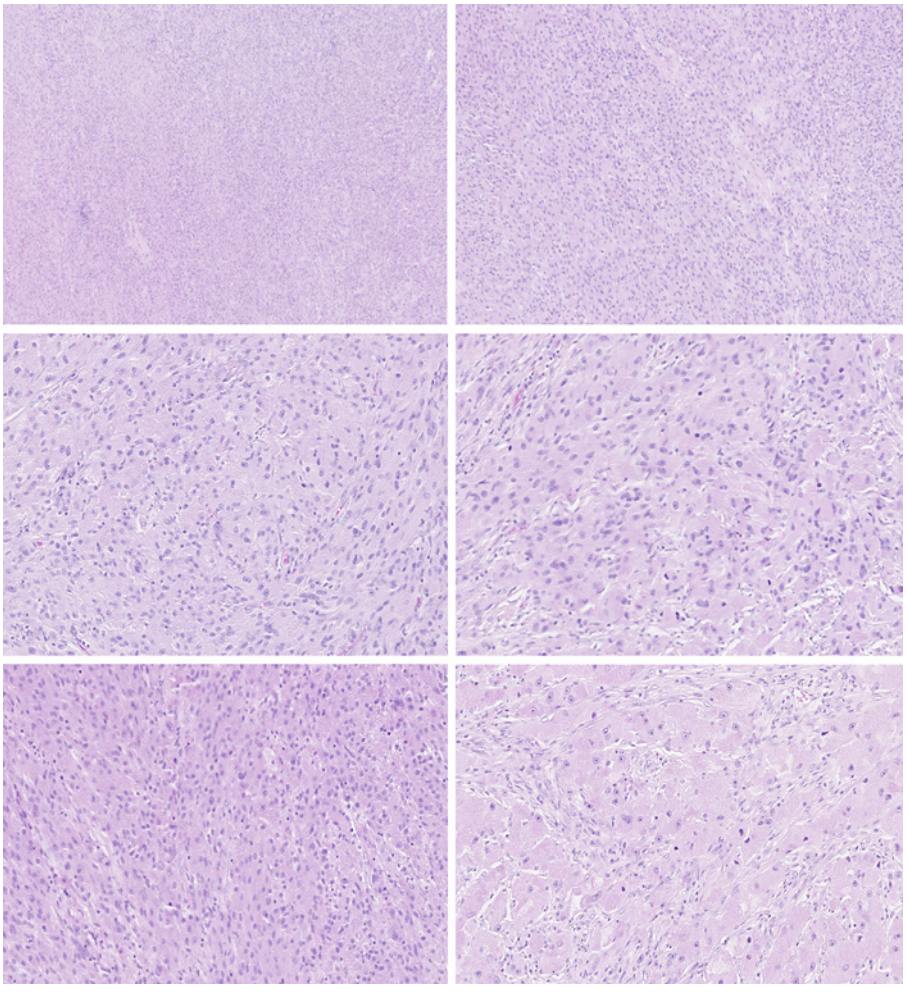

Fig. 4. Histopathological examination reveals a poorly defined mass. Sheets of cells or nests/ribbons separated by thin collagenous bands. Large polygonal or spindle cells and cell borders can be distinct. Pleomorphic nuclei with macronucleoli. Abundant eosinophilic cytoplasm with coarse granules (representing phagolysosome aggregates). Two mitoses/10 high-power fields. No necrosis.

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Table 1. Classification of granular cell tumor

Brooks et al. [12]	Fanburg-Smith et al. [13]	Nasser et al. [15]
1. A primary tumor with a diagnosis of GCT 2. High mitosis activity 3. Presence of wide nuclei and/or necrosis 4. The presence of metastasis.	1. Tumor necrosis 2. Spindle cells 3. Vesicular nuclei with preeminent nucleoli 4. Increased mitotic activity (>2/10 HPF) 5. High nucleocytoplasmic (N:C) ratio 6. Nuclear pleomorphism	1. Necrosis 2. Mitotic activity (>2 mitoses/10 high-power fields)
4 criteria: malignant GCT In the absence of metastasis, pleomorphism associated with both high index activity and necrosis is mandatory to confirm malignancy	≥3 criteria: malignant 1–2 criteria: atypical 0 criteria: benign	0 criteria: benign GCT >1 criteria: GCT with uncertain malignant potential

could be carried out. The patient was transferred to a palliative care unit and died a few weeks later.

Discussion and Literature Review

Abrikossoff's tumor or GCT is a relatively rare lesion, involving multiple anatomical sites, most frequently the head, the neck, and airways, and affecting especially women between 4th and 6th decades, with predominance in African Americans [2, 3]. However, a recent cohort analysis found that GCT can affect all groups and genders [8], even in children and some congenital cases [7]. Our patient was 77 years, which was particularly older than the median age of mGCT. The largest study to date has reported 157 previous cases of mGCT [9], with a median age of 51 years (IQ range: 38–62.5 years).

Our case concerns a recurrent GCT of the left thigh. According to Tsukamoto et al.'s [9] largest mGCT series, the thigh represents the second most frequent location after the trunk.

GCT is usually a benign, solitary, small, and painless lesion [2], with a high potential for postsurgical recurrence. The recurrence rate for benign GCT is estimated to be 2%–8% if surgical margin is negative and over 20% if it is positive [4].

GCT is almost always benign. However, a malignant form is encountered in 2% of cases [10], with a similar epidemiology to their benign counterparts, excepting their poor prognosis, with recurrence and metastatic dissemination typically within the first year of diagnosis [2]. The diagnosis of mGCT is particularly challenging because the distinction between benign and malignant tumor is often difficult, due to the lack of consistent histological and phenotypic criteria predicting a malignant behavior [7]. The presence of metastases is currently considered as the only unequivocal sign of true malignancy [11]. However, there is no clinical benefit from diagnosing a tumor as malignant after the occurrence of metastasis, given the poor prognosis of metastatic mGCT [8].

Brooks et al. [12] have proposed the first definition of mGCT, based on 4 criteria. In 1998, Fanburg-Smith et al. [13] published the first large series of GCT, subdividing them into malignant, atypical, or benign, according to the 6 histologic features (Table 1). The Fanburg-Smith et al. [13] histological definition is the most accepted for diagnosing mGCT [9].

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According to the Fanburg-Smith et al. [13] criteria, the primitive GCT of our patient was rightly considered as benign, as none of the 6 malignancy criteria was observed on histologic analysis. The recurrent GCT had 3 of the 6 malignancy criteria (spindle cells, large nucleoli, and nuclear pleomorphism), and thus can be considered as malignant. The malignant transformation of a benign GCT, rather than a de novo primary malignant tumor, as observed in our case, has been described in another report [14].

In order to establish more reliable criteria, some authors have proposed new classifications for GCT. Nasser et al. [15] considered that necrosis and mitotic activity are the 2 most highly characteristic criteria, and therefore classified GCT according to the presence of necrosis and/or mitotic activity (>2 mitoses/10 HPF) (Table 1). Only tumors classified as GCT with uncertain malignant potential occurring in patients with metastasis were considered malignant. Machado et al. [7] proposed to abandon the distinction between benign and atypical GCT and to classify tumors with histologically malignant features as "GCT with increased risk of metastasis," and those without malignant features as "GCT with almost no metastatic potential."

These new classifications are more inclusive and indicate the malignant potential of some lesions that would be considered as benign according to the previous criteria. However, they do not allow to establish the diagnosis of malignancy with certainty.

More recently, mGCT has been separated into 2 distinct variations [5]: the first one is based on clinical features, despite a benign histopathology, even if characterized by increased mitotic activity and mild nuclear pleomorphism. Thus, large size, rapid growth, and surface ulceration must be used as potential malignancy indicators [16]. The second variation is based on the Fanburg-Smith et al. [13] histologic features.

The histopathological examination of the primitive GCT of our patient showed an ulcerated exophytic nodule of 8 cm, with an ulcer measuring 4 cm. This lesion was excised 5 years ago, but a local recurrent lesion appeared after 2 years and rapidly increased in size to reach 6 cm at excision. The large size of and the ulceration of the primitive GCT should have alerted on its malignant potential. The local recurrence and the rapid growth are 2 other characteristics allowing to suspect an mGCT in our patient. Patients with larger GCT had poorer prognosis than patients with smaller tumors [17]. Therefore, tumors larger than 5 cm should raise the suspicion of malignancy [9].

FDG-PET/CT showed a hypermetabolic area in the left inguinal region, associated with hypermetabolic bone lesions and supra- and infradiaphragmatic lymph nodes. There are no available data in the literature about the most useful imaging approach for diagnosis and staging mGCT. FDG-PET may have a potential role in the management of patients affected by GCT, in particular for disease staging, excluding multiple localizations, and for diagnosis [18].

The PET-FDG/CT findings in our patient were highly suspicious for a metastatic GCT, confirming its malignant behavior, as most authors consider the presence of metastasis as the only unequivocal evidence of malignancy regardless of the histopathologic features [11]. Unfortunately, we failed to establish the similarity of the histological pattern between the primitive GCT and the metastasis observed in PET-FDG due to low yield of bone biopsy and the deterioration of the clinical condition of the patient, which prevented us from performing further samples.

Our patient had a recurrent GCT with clinical features suspected of malignancy (large size and rapid growth), in addition to malignant histologic features according to the Fanburg-Smith criteria, which led us to conclude to the diagnosis of an mGCT. PET-FDG showed multiple metastasis affecting bones and lymph nodes, which are among the most common metastatic sites for mGCT. In case of a metastatic mGCT, the lymph nodes, lungs, liver, and bones are the most affected sites [10]. Despite the absence of histologic evidence, we considered the lesions observed in the PET-FDG as metastatic of mGCT.

The prognosis of mGCT is extremely poor, with 32%–41% of recurrence and 50%–62% rate of metastasis, between 3 and 37 months after diagnosis [8]. Mortality reported in 3 years is approximately 30–50% for mGCT [4] and 100% at 5 years in case of metastatic mGCT [8].

Local surgical excision with clear margins remains the only recommended treatment for both benign and malignant GCT [8], in order to prevent local recurrence. Although the role of adjuvant radiotherapy for relapsing mGCT after a large excision has been mentioned in several publications, the benefit of adjuvant treatment (radiotherapy and chemotherapy) is still uncertain [7]. In case of metastatic mGCT, the therapeutic options seem limited, as chemotherapy/radiotherapy does not affect the prognosis positively [4]. Some recent findings of gene mutation in mGCT may provide new therapeutic agents. Otherwise, some authors described a response to pazopanib in patients with metastatic malignant GCT [7].

Conclusion

Abrikossoff GCT is benign in a large majority, but its potential malignancy should alert practitioners. The diagnosis of mGCT should be based neither on only histologic features nor on the presence of metastasis because of the challenging distinction between malignant and benign GCT and the extremely poor prognosis of metastatic mGCT. Large size and recurrence are the most important clinical features that can predict malignant behavior. Patients with a history of Abrikossoff tumor should have a close follow-up in order to monitor recurrence and malignant transformation.

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Statement of Ethics

This case report is exempt from ethics committee approval because it is a retrospective analysis of 1 clinical case and does not meet the criteria of research. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no relevant financial or nonfinancial interests to disclose.

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Author Contributions

Mohamed Tayeb Salaouatchi: conceptualization, acquisition of data for the work, and writing original draft preparation. Sandra De Breucker: supervision, review and editing, and approval for publication. Héloise Rouvière: review and editing. Véronique Lesage: revision.

Laureen Jeanne Armande Rocq: acquisition of data for the work and review and editing. Frédéric Vandergheynst: revision. Laetitia Beernaert: acquisition of data for the work and review and editing.

Data Availability Statement

All data underlying the results are available as part of the article. Further enquiries can be directed to the corresponding author.

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