

Giant Cell Tumor of Soft Tissues: A Case Report and Review of Literature

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Abstract

Background: Primary giant cell tumor (GCT) of soft tissue (GCTST) is an extremely rare slow-growing entity bearing a high similarity to conventional bone TCG (GCTB). The term, malignant tumor of giant cells of soft tissues have been reserved for histologically high-grade lesions. Although the gold standard remains surgical carcinological resection, bisphosphonates are beginning to prove their benefit in the treatment of GCTST.

Results and Discussion: A 37-year-old man came to the outpatient department of medical oncology with a painful swelling arising from his right elbow. Magnetic resonance imaging (MRI) of the right elbow was done and revealed a 19 cm × 7 cm, T1 and T2 hypointense lesion with significant postcontrast enhancement of calcified tissue nodules, distance extension report was negative. An echo-guided biopsy of the right elbow was performed. The anatomopathological examination showed a poorly delimited encapsulated tumor proliferation composed of sheets of histiocytic cells admixed with multinucleated giant cells dispersed uniformly among this tumor. Cells were embedded in a richly vascularized tissue. No significant nuclear pleomorphism or mitotic activity was appreciated. There were focal areas of osseous metaplasia. On the basis of these date, the diagnosis of giant cell tumor of low malignant potential was retained. Due to its intra-articular extension, the mass was judged unresecable. The case was discussed in a multidisciplinary consultation meeting indicating medical treatment with zoledronic acid given the unavailability of denosumab. After 8 monthly injections of zoledronic acid, a control imaging of the right elbow and forearm concluded to tumor stability.

Conclusion: GCTST is a slow-growing tumor known as soft tissue tumor. Numerous studies show the role of bisphosphonates when complete surgical excision cannot be performed. Further studies are needed to establish a standardized treatment protocol particularly in the context of inoperable large primary GCTST.

Keywords: Primary giant cell tumor of soft tissue; Bisphosphonates; Zoledronic acid

Introduction

Primary giant cell tumor (GCT) of soft tissue (GCTST) is an extremely rare slow-growing entity bearing a high similarity to conventional bone TCG (GCTB). The WHO classification recognized it as a distinct entity of low malignant potential, with a tendency to local recurrence while rarely metastasizing [1]. Clinically, it manifests as an asymptomatic mass with benign behavior, mainly located in the lower limb with thigh being the most common site, and trunk followed by the upper limb and the head and neck region [2]. It can be found in both superficial and deep soft tissues. It is frequently multinodular and consists of two main cell types: mononuclear stromal cells and multinucleated giant cells of the osteoclastic type. The term, giant cell tumor of soft tissue of low malignant potential, has been suggested regarded as the soft tissue analogue of giant cell tumor of bone, whereas the term, malignant tumor of giant cells of soft tissues have been reserved for histologically high-grade lesions.

Although the gold standard remains surgical carcinological resection, bisphosphonates are beginning to prove their benefit in the treatment of GCTST. Case reports describing the clinical and cytohistological features of this entity are exceedingly few. Altogether 200 cases had been reported until 2017. Here we report a case of TCGTM of low malignant potential arising in the right elbow and forearm treated with zoledronic acid with a brief review of the literature.

The aims of this study are to report this rare case of GCTST, to describe its clinical presentation, histopathological characteristics, treatment and assessment by referring to a review of the literature. We also wanted to underline the place of bisphosphonates and more particularly the zoledronic acid as a medical treatment of inoperable GCTST.

Case Report

A 37-year-old man came to the outpatient department of medical oncology with a painful swelling arising from his right elbow. The lesion was gradually increasing in size one month prior to presentation. No history of trauma, infection or similar swelling in any other part of body was present. On clinical examination, there was no restriction of movement of the right elbow. On palpation, it appeared to be a nontender, hard and non-pulsatile soft tissue mass fixed to the muscle and extended to the upper third of the forearm. Overlying skin was unremarkable. Magnetic resonance imaging (MRI) of the right elbow was done and revealed a 19 cm \times 7 cm T1 and T2 hypo-intense lesion with significant post-contrast enhancement of calcified tissue nodules. The mass was infiltrating soft tissues of the peri-articular muscles of the elbow and muscles of the right forearm which were: the anterior brachial, brachioradial, deep and superficial flexor of the fingers, supinator, lateral and medial triceps muscles. The tumor was extending up to the intra-articular space and was responsible for a bone erosion of the lateral condyle of the right humerus. There was no obvious extension to the median nerve and the radial artery. The distance extension report

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was negative. An echo-guided biopsy of the right elbow was performed. The anatomopathological examination showed a poorly delimited encapsulated tumor proliferation composed of sheets of histiocytic cells admixed with multinucleated giant cells dispersed uniformly among this tumor. Cells were embedded in a richly vascularized tissue. No significant nuclear pleomorphism or mitotic activity was appreciated. There were focal areas of osseous metaplasia. On the basis of these date, the diagnosis of giant cell tumor of low malignant potential was retained. Due to its' intra-articular extension, the mass was judged unrescuable. The case was discussed in a multidisciplinary consultation meeting indicating medical treatment be with zoledronic acid due to the unavailability of denosumab. After 8 monthly injections of zoledronic acid, a control imaging of the right elbow and forearm concluded to tumor stability.

Discussion

GCTST is a rare but clear distinct entity occurring primarily in the soft tissues which is histologically similar to GCTB [1]. There are few small series and case reports describing clinical and cytomorphological features of this entity. After a review of the literature we detected approximately about 200 cases of GCTST.

It was described for the first time in 1972 by Salm and Sissonswho coined the term "Giant-cell tumors of soft tissues" [3]. In the course of the same year, Guccion and Enzinger reported a more aggressive form of this same entity through the report of 32 cases considering that they are a related form of malignant fibrous histiocytoma [4]. In 1999, Folpe et al. proposed a histological sub-classification into two distinct forms according to nuclear atypia, pleomorphism and mitotic activity of the neoplastic component. The term giant cell tumor of soft tissue of low malignant potential, has been suggested for low histological lesions, having low mitotic activity as well as little nuclear atypia." [5].

Histological Features

Origin

The histogenesis of GCTST remains a mystery. Some authors suggest a mesenchymal origin by the occurrence of a spontaneous transformation of benign stromal cells. They supposed that, as a result of radiation or surgery, there is an alteration in blood flow that is responsible for the fusion of the circulating monocytes of giant cells [6,7].

Macro

The GCTST is well circumscribed and not encapsulated. It is often located in the peri-articular soft tissues as is the case of our patient. Its localization purely intramuscularly or subcutaneously, can be challenging to diagnose [8].

Micro GCTST

The tumor associates a mixture of mononuclear cells that are round to oval, and multinucleated osteoclastic cells. Both are encompassed in a richly vascularized stroma. In several studies, mitosis numbers in the benign GCTST range of 2 to 3/10 HPF to 9.5/10 HPF. Although not pathognomonic, the appearance of cellular and nuclear atypia, pleomorphism, high mitotic activity, necrosis and hemorrhage suggests malignant transformation (Figure 1). There is no bone involvement, but metaplastic bone formation is present in approximately 50% of tumors due to the secretion of transforming growth factors beta 1 and 2 by tumor cells. In GCTST, degenerative changes may occur such as stromal bleeding and accumulation of hemosiderin which are observed in 50% of cases, and foam macrophages as well as changes in aneurysmal bone cysts which are present respectively in 68% and 27% of cases. Our case lacked both changes [9,10].

Immunohistochemistry

The immunohistochemical study is not necessary for diagnosis, however it may provide additional information regarding the tumor. Similar to its' osseous counterpart, GCTST can shows positive stain for CD68, vimentin, tartrate resistant acid phosphatase (TRAP), cytokeratin and smooth muscle actin in both mononuclear cells and multinuclear giant cells (Figure 2). We did not perform this investigation in our case [11,12].

Differential diagnosis

It is important to differentiate GCTST from other tumors which can also exhibit pronounced giant cell component. The main differential diagnoses to be evoked are: giant cell tumor of tendon sheath (GCTTS), peripheral giant cell granuloma (PGCG), and giant cell malignant fibrous histiocytoma (MFH). As a GCTST, the GCTTS is composed of mononuclear histocytic cells and osteoclastic giant cells; however, the ratio between these two components is reversed between the two tumors since the GCTTS is characterized by a shortage of giant cells. Unlike GCTST, GCTTS is generally free of bone metaplasia and rich in dense fibrous tissue. PGCG originates only at the level of the periodontal ligament. It is therefore different from the GCTST by its location inside or on the gingiva or the alveolar crest. It is composed of giant cells with irregularly shaped nuclei, grouped around areas of necrosis and hemorrhage. MFH is readily multinodular with areas of necrosis and



Figure 1 (HE): Sheets of mononucleated histiocytic cells admixed with multinucleated giant cells dispersed uniformly among this tumor. No significant nuclear pleomorphism or mitotic activity.



Figure 2 (HE): Focal areas of osseous metaplasia.



Figure 3: Giant Cell tumor of the soft tissue (right elbow).

hemorrhage. It consists of tumor cells identical to those observed in the pleomorphic storiform variant with multinucleated giant cells of osteoclast type. These cells regularly dispersed in the cellular zones contain numerous small round nuclei with no abnormality (Figure 3). In about half of the cases, foci of osteoid or mature bone usually located at the periphery of the nodules are observed. MFH giant cells consists of multinucleated giant cells of osteoclast type. These cells regularly dispersed in the cellular zones contain many small round nuclei. In about half of the cases, there are foci of mature osteoid or bone usually located on the periphery of the nodules. It is different from GCTST according to the multinodular growth model, the presence of more marked cytological atypia, atypical mitoses and the presence of large areas of necrosis and hemorrhage. Therefore, it exhibits a very different biological behavior from the GCTST and a more pejorative prognosis [13-17].

Clinical presentation

The tumor is a slow-growing mass with an average duration of symptoms of six months, painless and mobile with well-defined boundaries. It does not involve tendons, muscles or bone structures. To our knowledge no etiological factor has been demonstrated. TSGTS affects the age group between 1 year to 89 years without sexual preference. In our study, our patient was 37-year-old. Numerous anatomical sites have been reported since 1972 and it has been described mainly at the extremities, trunk, abdomen and pelvis. Throughout the literature, it is noticed that the most common site appears to be the thigh and the region of the head and neck appears to be less frequently affected. Since the year 2000, other less common anatomical sites were described as breast, mediastinum, skin, ovary and intracerebral (Supplementary Table) [18-58].

Treatment

Conservative surgical resection with tumor free margin is the typical treatment for GCTST that assures a good prognosis with very low recurrence rate. Lung metastases has been reported in cases with positive surgical margins [54]. In surgically inappropriate cases, as is the case with our patient, no available treatment option was definitively effective in curing this disease. Microscopically, the GCT includes mononuclear and reactive neoplastic stromal cells and giant cells of the multinucleated osteoclast type. Based on these data, several studies have been conducted to demonstrate the role of bisphosphonates as a potentially attractive therapy, to reduce osteoclast activity and to control tumor growth. In this context, denosumab is the first medical treatment that proved its profit on GCT. It's a fully human monoclonal antibody that specifically inhibits the RANK ligand, which enhance osteoclast's activity. In recent years, several studies on Denosumab in patients with GCTB has shown objective clinical and histological changes in the tumor's behavior. David et al. conducted a phase II study in 35 patients with recurrent or unresectable GCTB. A tumor response was experienced by 30 patients (86%) [59,60]. Zoledronic acid (zoledronate) is a potentially attractive therapy for controlling tumor growth, particularly for tumors of giant cells rich in osteoclasts. The ability of zoledronic acid to reduce the activity of osteoclasts has been demonstrated *in vitro* by Cle'zardin et al. This team demonstrated that zoledronic acid had significant cytotoxicity in tumor cultures of giant stromal cells. In addition, it decreased the number of viable tumor cells in a dose-dependent manner [61,62].

Based on these results and on the great histological similarity between GCTB and GCTST, we treated our patient with zoledronic acid because denosumab was not available

Conclusion

GCTST is a slow-growing tumor known as soft tissue tumor equivalent of GCTB. Numerous studies show the role of bisphosphonates when complete surgical excision cannot be performed, particularly in the control of lesions of inoperative bone lesions. Given the great histological similarity between the two entities and the proven role of bisphosphonates in controlling osteoclast activity, further studies are needed to establish a standardized treatment protocol particularly in the context of inoperable large primary GCTST.

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