CASE REPORT

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# A case of giant cell tumor of the tendon sheath in an elderly patient: diagnostic difficulties and therapeutic options

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**Abstract**

Giant cell tumor of the tendon sheath (GCTTS) is a benign tumor with a high recurrence rate of up to 50%. The lesion may appear anywhere in the synovium; the nature of this tumor is still controversial, however recent data shows that tenosynovial giant cell tumors (TGCTs) could be clonal neoplastic tumors. Most lesions of GCTTS produce one or more discrete nodules, while the radiological features can include soft-tissue masses with or without bone destruction. In an effort to advance in the understanding of GCTTS pathogenesis, we decided broadly investigate the immunophenotypic profile, of a TGCT in a 69-year-old female patient.

***Keywords***: giant cell tumor, synovium, immunophenotypic.

## Introduction

Giant cell tumor of the tendon sheath (GCTTS), also known as localized pigmented villonodular synovitis (PVNS) [1], is a benign tumor of uncertain pathogenesis with a high recurrence rate of up to 50%. However, due to the possible malignant degeneration of the tumor, GCTTS is periodically called a semi-malignant tumor [2–5]. The lesion has been reported on all synovium, but has a clear preference for the in hand joints, as they make between 80% to 90% of cases (this tumor is known as the second most common tumor of the hand [6]), and infrequently in the knee and foot joints. The exact nature of this tumor is still largely unknown. Some speculate that GCTTS are a consequence of a reactive chronic inflammation process, while others think it originates in the synovial cell that form clonal neoplastic tumors due to overexpression of colony stimulating factor 1 (CSF1) [8]. Cell population in GCTTS is mostly polymorphous, varying from smaller mononuclear stromal cells with oval/reniform nuclei, to large histiocytoid cells, with an abundant eosinophilic cytoplasm and vesicular nuclei placed eccentric. Frequently, osteoclast-like giant cells, and xanthoma cells have been reported [9, 10]. In some cases, the tumors are composed of a monotonous stromal cells and just a limited number of giant cells [11].

The vast majority of GCTTS lesions produce at least one discrete nodule on the tendon sheath and/or small joints [12]. Radiological features include soft-tissue masses with or without bone destruction that are the cause of local periostitis or permeative bone invasion. As such, the best course of action is the incisional or excisional biopsy of the tumor [13, 14].

In an effort to advance in the understanding of GCTTS pathogenesis, we decided broadly investigate the immunophenotypic profile of a tenosynovial giant cell tumor (TGCT) in a 69-year-old female patient.

## Case presentation

A 69-year-old woman, predominantly right-handed tiller worker, presented at the Department of Rehabilitation and Physical Medicine, Emergency County Hospital, Craiova, Romania, with a localized right thumb tumor. Locally, the skin was ulcerated and at that moment, the patient indicated that this fullness has waxed and waned over the past two years, when he sought medical advice due to decreased sense of touch and weakness of the right-hand grip and right thumb pain with "popping and catching". The diagnosis, at the time, was ganglion cysts and physical therapy was applied, in order to lower the symptoms and the dimensions of the tumor. Following the therapy, the patient claimed an improvement regarding her decreased sense of touch and weakness of the right-hand grip. However, the dimensions of the tumor have not changed and the patient refused to be seen by a Plastic Surgery specialist, due to personal reasons. The patient had not returned to visit her physician in two years, neglecting the symptoms although he noted an increasing level of weakness concerning her right thumb that started in the last year. During the interaction, we were able to establish that there was bases for repetitive local trauma, but it was not sufficient to justify the increase in size of the metacarpophalangeal (MCP) joint, or the full history. No local signs of inflammation were noted. Routine blood work revealed only thrombocytopenia (125 000/μL). Ultrasound examination showed a solid heterogeneous mass of the right MCP I joint with local periostitis. The patient was directed to the Department of Plastic Surgery in order to ascertain the accurate diagnosis. The team

decided that surgery is the best course. After explaining, the patient consented to the surgery under general anesthesia. The procedure was started with a 3 cm incision directly on the volar front of the MCP joint of the right thumb and extended 0.5 cm distal and 1 cm proximal to the thenar musculature. Taking into account that the diagnosis was unclear, the hand was not forcefully exsanguinated and care was taken not to disrupt the fascial planes. A small portion of the mass was excised and sent as a frozen section for diagnostic purposes. A nodular, encapsulated, well-circumscribed mass was dissected, removed (1/1.5 cm, nine lobes mass) and sent for pathological evaluation, that revealed a lobulated and variegated tumor with tan, brown, golden, and yellow areas, depending on the amount of hemosiderin or foam cells in the tumors. A distinct lobulation was again discernible and the nodules were firm and elastic in consistency. The surgeons decided to extract the all tumor and biopsy fragments were send to a full immunohistochemical analysis.

After standard Hematoxylin–Eosin (HE) staining, cluster of differentiation (CD) 68, CD34 and CD38 immunostainings were performed. Appropriate positive and negative controls were made for each staining. Immunohistochemistry was performed with the help of a Labeled Streptavidin–Biotin (LSAB) 2 system, and the final reaction product was visualized through 3,3'-Diaminobenzidine (DAB) dihydrochloride. The examined tumor showed numerous giant cells containing a very large numbers of nuclei (Figure 1).

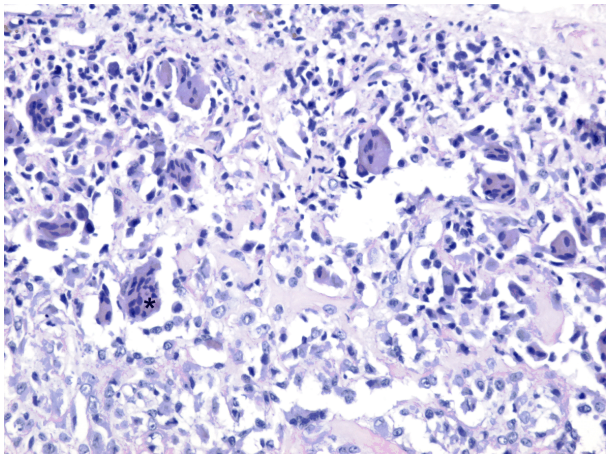


**Figure 1** – ***The giant cells contain very large numbers of nuclei, reaching more than 10 (*) (HE staining, ×200).***

Most of the cells had a slightly eosinophilic cytoplasm, while their nuclei varied both in number (ranging from two to 10 or more per cell) and size. It is unclear if some mononuclear cells had fused or contained phagocytic vesicles of other cells. The stromal cells were homogeneous mononuclear cells with round or ovoid shapes, large nuclei and indistinct nucleoli. As almost a hallmark of this type of GCTs, the nuclei of the stromal cells were identical to the ones contained by the giant cells.

Round, single nucleus cells with an eosinophilic cytoplasm arranged in sheets separated by fine bands of collagen form the basic cellular component (Figure 2A). The extracellular matrix is mostly made out of broad bands or sheets of collagen that showed hyalinization. The connective tissue was organized in bundles that separated cells in small groups with an alveolar pattern.

Immunohistochemically, the tumor showed spaces surrounded by either oval or flattened cells. Some of them had small tufts that could be projected into these cavities. One or more multinucleated giant cells were occasionally seen. This feature was showed using anti-CD38 antibody immunomarking for the differentiated vascular spaces from the alveolar cavities (Figure 2B). Anti-CD68 antibody immunomarking was strongly positive in the multinucleated giant cells (Figure 2C). Anti-CD34 antibody stains blood vessels in tissue sections, and, in our case was detected in normal vascular endothelial cells (Figure 2D) near to multinucleated giant cells.

## Discussions

Although the introduction of terms like localized PVNS or diffuse-type GCT has complicated the international nomenclature of this type of tumors, PVNS remains the main prototypic form of diffuse TGCT [11]. While the exact origin of GCTTS is still under discussion, it largely accepted that there is an associated with different processes varying from traumatic, inflammatory, reactive, metabolic, immune mediated causes all the way to neoplastic factors [15, 16].

The most widely accepted theory stipulates that there is reactive or regenerative hyperplasia associated with an inflammatory process [1], which arises as a consequence of chronic antigenic stimulation. Although, findings of aneuploidy in certain cases associated with demonstrated clonal chromosomal abnormalities strongly support a neoplastic origin [17], in the present case the only element to be considered, regarding the tumor's etiology is repeated microtraumatisms. Particularly to this case was the age of the patient, at the beginning of the disease, whilst the tumor most commonly occurs in patients aged 30–50 years in our case the patient was 69, which is fairly uncommon [18]. Although, is probably that the MCP articulation, where the tumor occurred, had already osteoarthritic injuries, the ultrasonography in this case was not able to provide the diagnosis regardless of the advances made in the field [19].

The overall features of the lesion in our study are similar to previous studies, starting with the dimensions of 0.5 cm to 4 cm previously noted to the lobulated nature of the process [20]. One major distinction was the intraosseous invasion that, in our case, was not present. This may be explained in part by the fact that the tumor occurred in hand small joint and not a large one that are noted to be more invasive [21].

The microscopic appearance of GCTTS was variable, closely linked with the proportion of mononuclear and multinucleate giant cells, foamy macrophages, siderophages and the amount of stroma. Whereas osteoclast-like giant cells are common in this type of tumor [9, 10], the reasons for osteoclast-like giant cells accumulation in GCTTS is still largely unclear. The production of osteoclasts appears to be a consequence of local production of cytokines varying from transforming growth factor $\beta$1 and macrophage CSF to parathyroid hormone related peptide, all resulting in mononuclear cells fusing and forming giant cells with osteoclast phenotype and morphology [22].

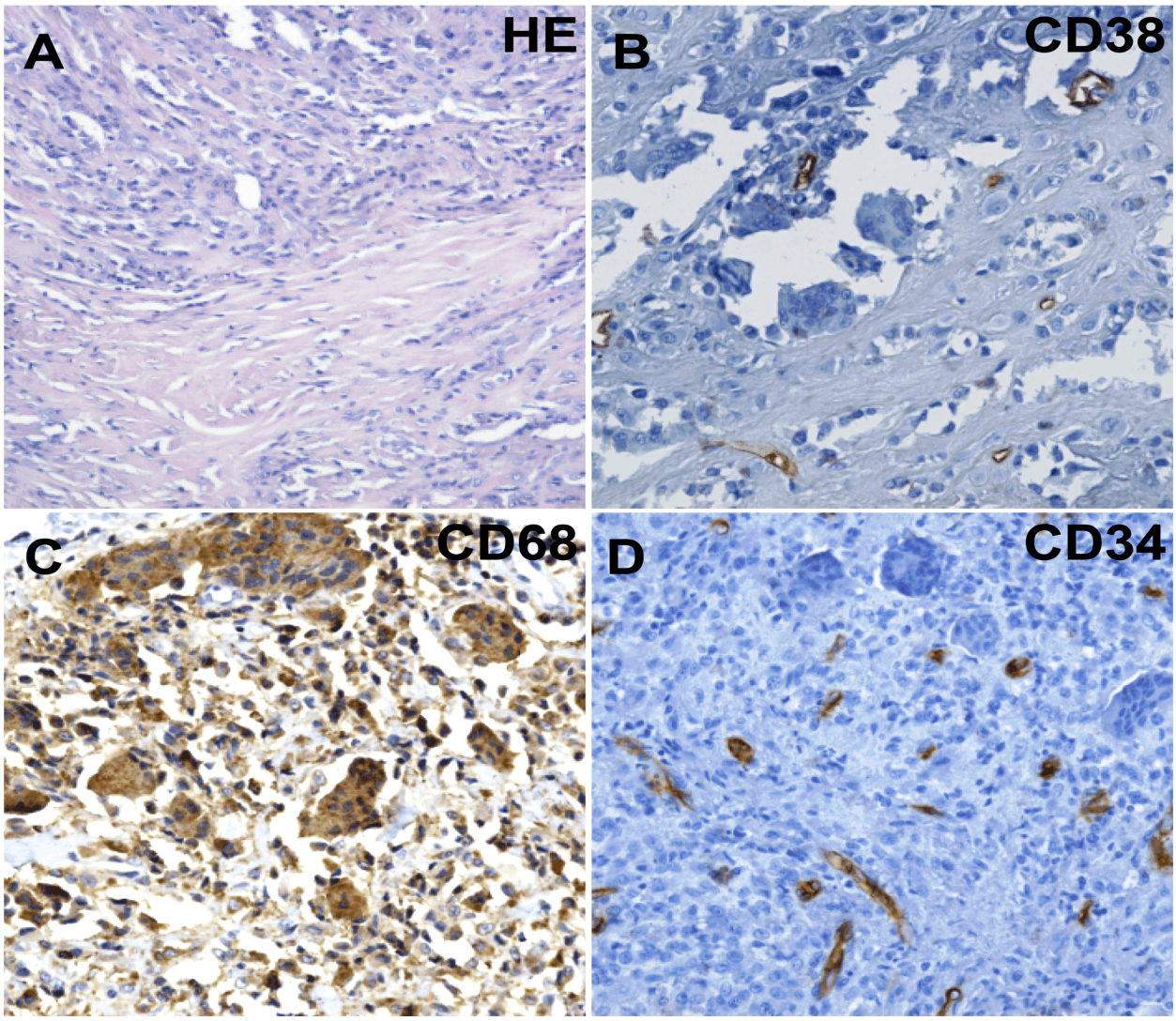


**Figure 2** – ***TGCT with (A) fibrous collagenous tissue (sclerosis) and (B) few CD38-positive cells. (C) Most of the multinucleated giant cells were CD68-positive as well. (D) The TGCT was found to have a normal vascularization, as we were not able to identify a large number of CD34-positive cells in the tumor. HE staining: (A) ×100. Anti-CD38 antibody immunomarking: (B) ×200. Anti-CD68 antibody immunomarking: (C) ×200. Anti-CD34 antibody immunomarking: (D) ×200. TGCT: Tenosynovial giant cell tumor; HE: Hematoxylin–Eosin; CD: Cluster of differentiation.***

The diagnosis of GCTTS may be difficult, however one should always consider this diagnosis for any subcutaneous masses over the digit, especially if it exhibits well-circumscribed multinodular aspect. Painless and slowly increase in size over a long time are also known to be characteristics of GCTTS. The emergence of the local pain and the superficial ulcerated skin are atypical. Considering the concerned case, the most probable cause is represented by the improper strain of the joint where the tumor was present. However, this characteristic is not unique only to GCTTS; complaints of pain at the MCP joint could be associated with any of the following: Dupuytren's contracture, sesamoid bone anomalies, focal dystonia, hysteria, trigger finger, post-traumatic tendon entrapment on the metacarpal head, MCP joint osteoarthritis, MCP joint sprain.

As surgical therapies become more advanced, the non-surgical approach of GCTTS been abandoned. However, the incidence of local recurrence is extremely variable, ranging from 9% to 44% [23, 24]. Although the classic reason for these recurrences was either an incomplete removal of the tumor, recent studies demonstrating cytogenetic abnormality in the form of trisomy 7 and autonomous growth. Case reports of metastatic GCTTS or local recurrence have certainly raised the possibility that GCTTS could be classified as cancer [20]. Interestingly, a new technique using radiotherapy as an adjuvant modality to prevent local recurrence has been described with promising results [25]. In our case, the patient received only a surgical treatment and at the moment she is undergoing medical rehabilitation. The patient has been informed of the potential relapse and is monitored.

## Conclusions

Although GCTTS is the second most common solid, soft-tissue lesion of the hand it is still unknown if it is a true neoplasm or a reactive origin illness. As such, one should always consider it in the differential diagnosis for all masses present in the hand and legs. Prior to surgery, the clinical difference between a malignant or benign mass is usually very difficult in this cases, but an immuno-

histochemistry diagnosis show be easy to make. Surgical removal remains the gold standard for GCTTS. The particularities of the above-discussed case are determined by the patient's age, the localization of the tumor within the MCP pollex joint and the presence of the superficial ulcerated skin. Even if the diagnosis could have been oriented to a different type of tumor, the microscopic analysis was able to assign the certain diagnosis. Although there are not any concrete data regarding the role of the recovery treatment (local electrotherapy), it is considered suitable until a surgical approach of the case. The reasoning behind this assumption consists in the intention of decreasing the local symptoms caused by the tumor.

**Consent**

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

**Authors' contribution**

Daniela Matei, Simona Pătru, Liliana Pătru and Iulia-Rahela Marcu analyzed and interpreted the patients' examination data; George Laurenţiu Pătru performed the histological examination of the specimens from the patients. Adrian-Costin Bighea and Daniela Matei represented major contributors in writing the manuscript. All authors read and approved the final manuscript.

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