Tenosynovial Giant Cell Tumors Lacking Giant Cells: Report of Diagnostic Pitfalls

Yi Ding1, Jennifer E. Griffin2, Meera Raghavan3, Hairong Xu4, Evita Henderson-Jackson2,5, and Marilyn M. Bui2,5

1Department of Pathology, Beijing Ji Shui Tan Hospital, Peking University, Beijing, China, 2Department of Anatomic Pathology, Moffitt Cancer Center, Tampa, FL, USA, 3Department of Radiology, Moffitt Cancer Center, Tampa, FL, USA, 4Department of Orthopedic Oncology Surgery, Beijing Ji Shui Tan Hospital, Peking University, Beijing, China, and 5Sarcoma Department, Moffitt Cancer Center, Tampa, FL, USA

Abstract. Tenosynovial giant cell tumors are a group of neoplastic disorders that involve synovium-lined tendon sheaths, synovial joints, and adjacent soft tissue. They are divided into localized and diffuse subtypes. TSGCTs have well-established clinical and histological diagnostic criteria; however, the subtypes and nomenclature can be confusing. They also pose diagnostic challenges when they occur in atypical locations or without multinucleated giant cells. With the possibility for systemic targeted therapy in relapsing pigmented villonodular tenosynovitis and diffuse-type giant cell tumor, accurate diagnosis and subtyping of TSGCTs is increasingly important. We report two cases of TSGCTs in order to elucidate the diagnostic nomenclature, clinicopathological features, differential diagnosis, and diagnostic pitfalls. Recent advancements in the pathogenesis and targeted therapy of TSGCTs are also discussed.

Introduction

Tenosynovial giant cell tumors (TSGCTs) were first introduced by Jaffe et al. in 1941 [1]. TSGCTs involve the synovial joint, tendon sheath, and the soft tissue near the joint. They are grouped into intra-articular and tendon sheath/bursa tumors. They are also described as either localized or diffuse [2-8]. Giant cell tumor of the tendon sheath (GCTTS) is the most common TSGCT [6, 9]. It is a localized form also known as nodular tenosynovitis. Localized TSGCTs may occur at any age but are usually diagnosed in patients between 30 and 50 years of age, and are more common in women [2]. They present as discrete nodules primarily affecting the tenosynovium of hands and feet (75% are in digits). The nodule is grossly well-circumscribed and encapsulated. The cut section shows a lobulated and tan-brown appearance. The tumor is composed of a polymorphous population of cells including osteoclast-like giant cells, larger mononuclear histiocytes, smaller mononuclear stromal cells, and macrophages that either engulf fatty content (xanthoma cells or foamy cells) or are hemosiderin-laden (pigmented) [2]. Lymphoplasmacytic infiltration is usually a minor component. Fibrous and collagenous stroma can be seen. This tumor has an indolent clinical course. When treated with simple excision, it has a recurrence rate of 4-30% [2,6,8,11].

Another localized TSGCT presents as an intra-articular solid nodule. It is rare but similar to GCTTS in its histology and indolent behavior. When it is called localized pigmented villonodular tenosynovitis (PVNS) [9], this nomenclature can be confusing because this tumor typically does not have the villonodular appearance and the clinical course is not aggressive. Conventional pigmented villonodular tenosynovitis (PVNS) is a diffuse-type TSGCT [3,9,11]. It is intra-articular and typically does not involve the soft tissue. It is rare, with an incidence of 1.8 per million, and occurs in adults averaging 35 years of age, with a slight female predominance. It typically involves large weight-bearing joints such as the knee (75-80%) and hip (15%) [2]. It presents as multiple, ill-defined, intra- or peri-articular nodules. Cortical erosion and subchondral cysts are usually present. Grossly, it has a characteristic red brown villonodular appearance. Histologically the tumor has the cellular components of all other
TSGCTs, in addition to the profound villous arrangement with synovial lined clefts. This tumor is locally aggressive. Even when treated aggressively with wide local excision, total synovectomy and arthroplasty, multiple recurrences can occur in 30-50% of patients.

Diffuse-type giant cell tumor (GCT) is an invasive form of diffuse-type TSGCT with extra-articular component [9]. The hallmark is the soft tissue involvement, regardless of whether the tumor arises from the joint or soft tissue. It shares many histological features of conventional PVNS; however, this tumor involves extra-articular soft tissue and is clinically much more aggressive. For practical purposes, the term of diffuse-type TSGCT includes PVNS (intra-articular) and diffuse GCT (extra-articular with or without involvement of the adjacent joint). These tumors are regarded as locally aggressive but non-metastasizing. While most TSGCTs are benign, rare cases of malignancy have been reported [3,7,12]. The identification of malignant histology such as nuclear pleomorphism, atypical mitosis, and tumor necrosis are key to this diagnosis. Increased mitotic activity can be seen in benign TSGCT; however, the presence of atypical mitotic figures are indicative of a malignant process. In addition to the sarcomatous histology of a malignant TSGCT, the tumor can also metastasize and be lethal.

In conjunction with clinical and radiological information, by following the above generally accepted diagnostic criteria, TSGCT can be diagnosed and subtyped accurately from small biopsy specimens in most cases. However, we have encountered two challenging cases of TSGCTs.

The following two cases were evaluated and reported in compliance with the University of South Florida’s Institutional Review Board Policy #311.

**Case 1.** A 63-year-old female presented with a one-year history of debilitating low back pain. Physical

---

**Figure 1.**

A. Spine-Axial post contrast fat suppressed T1-weighted sequence image demonstrates rounded lesion adjacent to the left L4-5 facet in the paraspinal tissues. The lesion demonstrated low to inoaint T1 signal and intermediate to high T2 signal. There was associated involvement of the adjacent bone (not shown). B. A close-up photograph of the population of mononuclear cells highlights their cytologic features. The mononuclear cells have round to ovoid, uniform nuclei, inconspicuous nucleoli and moderate eosinophilic cytoplasm. (hematoxylin-eosin, original magnification x400). C. The histiocytoid mononuclear cells demonstrate positive staining for CD163. (immunostain, original magnification x400). D. The mass shows a subtle pseudoalveolar architecture revealing loosely cohesive mononuclear cells with a histiocytic appearance and smaller plasmacytoid appearing cells focally attached to fibrous septa. (hematoxylin-eosin, original magnification x200).
examination revealed a palpable soft tissue mass in the left paraspinal musculature of L4/L5. Bilateral lower extremities from L4 to S1 had intact neurovasculature. MRI revealed a 6x5x4 cm, well demarcated, enhancing soft tissue mass adjacent to the left L4-L5 facet (Figure 1A). CT-guided fine needle aspiration and core biopsy were performed. FNA cytology showed mononuclear cell proliferation with atypical plasmacytoid changes. The flow cytometry analysis showed no phenotypic evidence of lymphoma, plasma cell dyscrasia, or hematopoietic malignancy. The biopsy specimen revealed a mononuclear cell proliferation with crushed artifacts and scattered plasmacytoid cells. No mitoses or necrosis were identified. A preliminary diagnosis was a benign neoplasm of unclear lineage. Immunohistochemical studies were done with appropriate controls. The tumor cells were positive for vimentin and CD68, focally positive for CD56, while negative for synaptophysin, neuron specific enolase (NSE), cytokeratin AE1/AE3/CAM5.2, CD20, CD3, CD138, S-100, and pan-melanoma. A diagnosis of benign histiocytic neoplasm was favored. Two months later, the lesion was completely excised. Intraoperative observation was that the tumor was capsulated without any invasion of soft tissue. The mass was 7x5.5x1.5 cm. Grossly, it was well-circumscribed, encapsulated, tan-yellow, lobulated, and rubbery. Histologically, it was cellular and composed of lymphocytes, plasmacytoid cells, and larger mononuclear cells resembling histiocytes (Figure 1B). There was an absence of osteoclast-like multinucleated giant cells, xanthoma (foamy) cells, or hemosiderin. Mitosis was infrequent. The differential diagnoses included hematopoietic neoplasm, melanoma, myoepithelial tumor, neuroendocrine tumor, and TSGCT. Flow cytometry of the resection specimen revealed a population of cells of mononuclear cytotype with no cytological or phenotypical evidence of malignancy. Immunohistochemical studies were done with appropriate controls. The large mononuclear cells were positive for vimentin, CD68, CD163 (Figure 1C) and focally positive for S-100, while negative for pan-melanoma, synaptophysin, desmin, actin, WT-1, cytokeratin AE1/AE3/CAM5.2, CK7, CK20, CD45, CD99, and CD138. This immunostain pattern confirmed that the tumor was of histiocytic/monocytic origin. Closer examination revealed focal alveolar or pseudoglandular appearance (Figure 1D). Giving the peri-articular location, the overall microscopic features, and the immunohistochemical findings, the diagnosis of an unusually cellular form of localized GCTTS was rendered. The tumor did not have any malignant features. The surgical margin was negative. It has been 41 months since diagnosis, and the patient has no evidence of recurrence.

Case 2. A 50-year-old female presented with a mass on the dorsal aspect of the left foot that had gradually increased in size over a six-month period and was associated with significant pain. The patient had previously experienced decreased sensation in the left foot. Upon physical examination of the left lower extremity, a palpable 1x1 cm mass was identified over the fourth metatarsal. MRI showed a homogeneously enhancing soft tissue nodule involving the head of the fourth metatarsal, closely associated with the metatarsal phalangeal joint (Figure 2A). Ultrasound-guided needle biopsy specimen showed atypical mononuclear cells admixed with lymphoplasmacytoid cells and collagenous stroma. Differential diagnoses included hematopoietic neoplasm, as well as histiocytic sarcoma, melanoma, carcinoma, and TSGCT. Immunohistochemical studies were done with appropriate controls. The tumor cells were positive for CD68, CD163, and S-100, focally and weakly positive for Factor XIII, while negative for cytokeratin AE1/AE3/CAM5.2, melan A, pan-melanoma, CD45, CD15, CD30, MPO, CD3, CD10, CD20, CD34, and CD138. Ki-67 was positive (3+) in more than 5% of the nuclei of tumor cells. These findings were suggestive of an atypical histiocytic proliferation. The possibility of a histiocytic sarcoma could not be excluded. After multidisciplinary review of the case, the patient opted for radiation therapy, and the mass was subsequently deemed appropriate for surgical resection. Grossly, the resection specimen showed an encapsulated, well-circumscribed mass measuring 2.5x1.5x0.9 cm. It had smooth cut surfaces and a yellow-tan appearance. Histologically the tumor was composed of an admixture of mononuclear histiocytoid cells, mononuclear stromal cells, foamy cells, lymphoplasmacytoid cells, and pigment-laden histiocytes. Only rare and scattered multinucleated giant cells were noted (Figure 2B). There were no significant cytological atypia, necrosis, or atypical mitoses seen. Immunohistochemical studies revealed tumor cells positive for CD68 (Figure 2C) and CD163, while negative for S-100, HMB-45, pan-melanoma, p63, p53, and CD1a. In 20% of the nuclei of tumor cells, Ki-67 was positive (3+). These findings confirmed histiocytic origin without evidence of malignancy. Although there was a paucity of multinucleated giant cells, considering the location in the digit and the overall characteristic histological features, this tumor was most consistent with a localized TSGCT. The patient has been disease-free for 12 months.

Discussion

Multinucleated giant cells are a major diagnostic clue for TSGCTs, in addition to a constellation of other histological features. It can be difficult to
Diagnosis of TSGCTs lacking giant cells

distinguish between localized and diffuse TSGCTs from a small biopsy sample. The histologic features must be considered along with the clinical and radiographic findings to determine the subtype [6, 13]. When the characteristic osteoclast-like giant cells are devoid, immunohistochemical studies can be useful. The larger mononuclear cells are positive for clusterin [13]. Desmin staining highlights a population of cells with dendritic features in 45 to 80% of cases [13]. The histiocyte-like cells (large, small, or multinucleated) are positive for histiocytic/macrophage markers like CD68, CD163, and CD45 [6, 7].

Although the World Health Organization (WHO) classifies TSGCT as a benign, so-called fibrohistiocytic tumor, there was a debate regarding whether it is a true neoplasm or a pseudoneoplastic inflammatory response to soft tissue trauma [7, 13]. It is currently accepted as a neoplasm, a hypothesis supported by the presence of clonal chromosomal aberration (translocations involving chromosome 1p11-13) and the overexpression of macrophage colony-stimulating factor 1 receptor (CSF1R) in these lesions. Recently, TSGCTs have been characterized by the discovery of COL6A3-CSF1 gene fusion derived from a recurrent chromosomal translocation (1: 2) (p13;q37) [5, 6, 11, 14, 15]. It is noted that the CSF1-driven neoplastic cells represent the mononuclear stromal cells that account for a small proportion (2-15%) of cells within the tumor. Most cells within the tumor are non-neoplastic and inflammatory in nature.

For these two cases, the diagnosis of localized TSGCT was not obvious due to the patients’ older age at presentation as well as the tumors’ uncommon location and lack of multinucleated giant cells. In addition, the predominant component is the plasmacytoid-appearing mononuclear cells whose origin is not readily identifiable. Each of these factors is discussed below.

Older age at presentation. Localized TSGCTs may occur at any age but are usually diagnosed in patients between 30 and 50 years of age, and are more common in women [6, 13].

Uncommon Location. Localized TSGCTs primarily affect the tenosynovium of the hand. Approximately 85% occur in the fingers, in close proximity to the synovium of the tendon sheath or interphalangeal joint. Other sites include the wrist, ankle/foot, knee, and rarely, the elbow, hip, and thoracic spine [10]. Diffuse intra-articular lesions affect predominantly the knee (75% of cases), followed by the hip (15%), ankle, elbow, and shoulder [2, 9]. Extra-articular tumors most commonly involve the knee, thigh, and foot [7]. Axial skeleton location of TSGCT is very rare, and only one other case involving the thoracic spine was reported with classic histological features of localized GCTTs [16]. The primary bone lesions at this location include osteoblastoma, bone cyst, and giant cell tumor of bone. However, when it is primarily an extrasosseous soft tissue lesion excludes the above differential diagnoses. Although other soft tissue tumors are more common, TSGCT should also be considered in the differential diagnosis in an older patient with a lumbar paraspinal soft tissue mass.
Lack of multinucleated giant cells. Because of the lack of osteoclast-like giant cells, these specimens were thought to be other tumors, such as histiocytic sarcoma, which is a malignant neoplasm that usually occurs in lymph nodes, skin, and the gastrointestinal tract. They are composed of cells that morphologically and immunohistochemically resemble mature tissue histiocytes [8]. Histiocytic sarcomas were formerly designated as true histiocytic lymphoma, which is thought to be derived from mononuclear phagocytic cells (macrophages and dendritic cells) or histiocytes. In rare cases, histiocytic sarcoma can be periarticular, and its multinodular appearance is grossly very similar to TSGCT. This morphological similarity, combined with the histological similarity between biopsy specimens, adds to the difficulty in distinguishing between histiocytic sarcoma and TSGCT. CD68 and CD163 are representative biological markers for TSGCTs [6,8]. However, CD68 and CD163 can be focally positive in other histiocytic cell tumors because these lesions include aggregated histiocytic cells [6,12]. Some claim that in histiocytic sarcoma, CD163 highlights both the mononucleated cells and multinucleated giant cells. In TSGCTs, CD163 is mostly positive in mononucleated cells [6,8].

Mononuclear cells which are plasmacytoid-appearing. CSF1-driven neoplastic cells represent the mononuclear stromal cells which usually account for a small portion of the cells within the tumor intermixed in a background of non-neoplastic and inflammatory cells [5]. When these mononuclear stromal cells have a plasmacytoid appearance, the differential diagnoses include melanoma, neural and neuroendocrine tumor. Immunohistochemical studies are helpful in characterizing the tumor cells of histiocytic origin. When the histologic features were considered along with the clinical and radiographic findings, the diagnosis of TSGCT became clear.

Another two lesions to include within the differential would be giant cell tumors (GCTs) of the bone with extraosseous extension and giant cell tumor of soft tissue (GCT-ST). It is easy to differentiate these lesions from TSGCTs because TSGCTs arise from the joint, while giant cell tumors of the bone arise from the epiphysial/meta-epiphysial part of the bone, and extend to the articular surface in some cases [6]. While the GCTTSs are morphologically similar to GCTs of bone, PVNS differs from GCT of bone by virtue of their characteristic villonodular appearance. Most importantly, GCT of bone is a clinically, radiologically, genetically, and histologically distinct entity. GCT-ST usually occurs in superficial soft tissue of the upper and lower extremities in the fifth decade of life. Histologically, it displays a strikingly multinodular architecture with various sizes of nodules. Fibroma of the tendon sheath comes from the same general location as TSGCTs, but prominently consists of hyalinized collagen with paucinuclear mononuclear cells [16]. TSGCTs begin as highly cellular lesions, but if left untreated over time, they may become more burned out and resemble a fibroma. Acral myxoinflammatory fibroblastic sarcoma (MIFS) can involve or arise from synovium. Aggregates of macrophages and uniform mononuclear cells with foci of hemosiderin deposition closely resemble TSGCTs. However, TSGCTs lack the primary cytological atypia and the acute inflammatory cells seen in MIFS. Some small synovial sarcomas of the hands or feet may be deceptively bland-appearing and confused with TSGCTs. Immunohistochemical stains for epithelial markers and molecular study for hallmark signatures can assist in this differential diagnosis [6].

Classical hemosiderotic synovitis shows hemosiderin deposition in synoviocytes and subsynovial tissue. Although this is a reactive process, it can look like a synovial neoplasm. Polyarticular synovitis can be seen in proliferative synovitis, rheumatoid synovitis, or degenerative synovitis. Because of their papillary synovial hyperplasia, they may present with a profound villonodular appearance that mimics PVNS.

In a review of recent literature, a standardized treatment of TSGCTs is controversial and limited due to differences in location, disease extent, and small number of patients in reported case-series. Heijden, et al [13] recommend localized TSGCT be treated with an open surgical resection with negative surgical margin rather than arthroscopic treatment to prevent possible contamination and potentially reduce the low recurrence risk. Treatment for the diffuse-type TSGCTs, i.e. PVNS or diffuse-type GCT, usually consists of an open complete synovectomy, and has a 20-30% recurrence rate. In
certain cases without extra-articular involvement, the placement of intra-articular radioactive colloids can be used as local adjuvant therapy, although there is scant reported evidence of benefit. Patients that present with diffuse extra-articular joint disease should receive an open complete resection. At times it may be difficult to achieve complete resection and external beam radiation can be utilized for adjuvant treatment; however, it is not advocated in the joints of the hand and foot. In cases where disease is unresectable, radical resection and joint reconstruction followed by radiotherapy is recommended, but neo-adjuvant systemic therapy using CSF1R inhibitors (e.g. imatinib, nilotinib) can be considered especially if radiotherapy is not an option [13]. Further prospective studies are warranted in the use of systemic targeted therapy as neoadjuvant therapy. In cases of recurrences, extensive synovectomy and total arthroplasty with or without external beam radiation are sometimes required [4,17,18].

For relapsed or metastatic PVNS/diffuse-type GCT/ diffuse-type TSGCT, there is no established medical therapy. However, tyrosine kinase receptor inhibitor therapy has shown some promise [19]. SF1R inhibitors are clinically available for surgically-resectable cases. In order to select patients for targeted therapy, an accurate diagnosis of diffuse-type TSGCT is essential. For example, we recently encountered a consultation case that was a non-specific, multifocal synovitis that mimics PVNS. Our review changed the original incorrect diagnosis and deemed the patient was not qualified for targeted therapy trial for PVNS. We cannot emphasize enough that although the current literature recognizes that a small subset of cases show a paucity of osteoclastic giant cells, this remains a practical diagnostic pitfall.

In summary, we report two cases of localized TSGCTs that are morphologically unusual. The clinicopathologic features, diagnostic nomenclature, differential diagnosis, diagnostic pitfalls, and most recent advancement in the understanding of targeted therapy of TSGCTs were discussed. In order to accurately diagnose and subtype this disease, it is vital to closely examine the constellation of clinical, pathologic and radiologic findings, especially when dealing with small biopsy specimens. Be aware of the therapeutic indication for PVNS and select candidates carefully.

Acknowledgement

The authors thank Ms. Angie Reagan at the Moffitt Cancer Center Graduate Medical Education Office for her assistance in submitting the manuscript and her dedication to her work.

References