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CORRESPONDENCE

A hyalinised tenosynovial giant cell tumour with absence of giant cells posing a diagnostic challenge

To the Editor,

Tenosynovial giant cell tumour (TGCT) is a soft tissue neoplasm that arises from the synovial lining of joints, bursae and tendon sheaths.[1] TGCT is classified based on its clinical presentation and biological behaviour as localised (L-TGCT) or diffuse (D-TGCT), the former previously known as a giant cell tumour of the tendon sheath or localised nodular tenosynovitis, and the latter previously known as pigmented villonodular synovitis (PVNS).[2]

L-TGCT usually occurs between the ages of 30 and 50 years with a predilection for females. It tends to be extra-articular and mainly involves the digits (85% of cases), located near the tendon sheaths or interphalangeal joints. L-TGCT is a benign neoplasm that presents as a painless, slow-growing mass coming to clinical attention weeks to years after onset.[3] In contrast, D-TGCT usually affects young adults less than 40 years of age with no gender predilection.[4] It is predominantly intra-articular and mainly affects large joints such as the knee (75% of cases), hip and ankle.[5] D-TGCT is locally aggressive and destructive given its infiltrative growth pattern and patients typically present with articular complaints including joint swelling, restricted range of movement or instability.[6] Rarely, D-TGCT has been reported to undergo sarcomatous transformation with a high rate of local recurrence and distant metastasis.[7,8] A case of metastasising D-TGCT has also been documented.[9]

The pathogenesis of TGCTs is thought to be a 'landscape effect' attributed to a minor population of neoplastic cells with aberrant expression of colony-stimulating factor 1 (CSF1) leading to the recruitment of CSF1-receptor-expressing macrophages and inflammatory cells which form the majority of the tumour milieu.[10] The overexpression of CSF1 by neoplastic cells is due to a *COL6A3*::*CSF1* gene fusion resulting from a t(1;2)(p13;q37) rearrangement, which occurs in approximately 60% of TGCT.[10,11]

Histologically, TGCTs consist of neoplastic large epithelioid mononuclear cells with eccentric nuclei and abundant eosinophilic cytoplasm, small histiocytoid cells, multinucleated osteoclast-like giant cells, foamy histiocytes, lymphocytes and variable stromal hyalinisation and haemosiderin deposition.[3] Immunohistochemically, the large neoplastic cells are positive for clusterin and D2-40 and focally positive for desmin which highlights their dendritic processes, while the small histiocytoid cells are diffusely positive for CD68 and CD163.[2,3] L-TGCTs are well-circumscribed while D-TGCTs have an infiltrative growth pattern with more conspicuous cleft-like spaces.[2]

Several histological variants have been reported including TGCTs with extensive chondroid metaplasia[11] and myxoid change.[3] While the relative prognosis of these variants is unknown, their significance lies in distinguishing them from other histological mimics. Here, we report a case of a 49-year-old male with TGCT of the right calf showing extensive stromal hyalinisation and absence of giant cells, resulting in a diagnostic challenge, and discuss features which distinguish it from other differential diagnoses.

A 49-year-old male with no notable past medical history, presented with a progressively enlarging lump on the right lower limb of 3 weeks' duration. Physical examination revealed a 3×3 cm soft tissue mass over the distal lateral aspect of the right calf with no surrounding skin changes. Given its superficial location and absence of worrisome features, no imaging was performed. The patient was counselled and opted for surgical excision. Intraoperatively, the mass measured 2×2 cm and was not adherent to the underlying muscle fascia. The entire mass was excised without gross residual disease. Macroscopic pathological examination showed a firm mass measuring 1.5×1.0 cm. Histological examination revealed a mass within the subcutaneous tissue with vaguely nodular architecture and composed of a moderately cellular population of neoplastic epithelioid cells, set within a hyalinised eosinophilic stroma (Fig. 1A). Interspersed areas of reactive changes including spindled fibroblastic proliferation, fibrosis, capillary proliferation and entrapped fat necrosis were present (Fig. 1B). The epithelioid cells showed abundant dense eosinophilic cytoplasm, enlarged eccentrically-placed nuclei and prominent nucleoli (Fig. 1C). Scattered small histiocytoid cells were seen within the stroma. Some areas of dense hyalinised stroma mimicked osteoid matrix (Fig. 1D). The classic ladybird cells were not identified. No significant cytological atypia or mitotic activity was seen. No multinucleated osteoclast-like giant cells, foamy histiocytes or haemosiderin deposition were present. Tumour was present at the resection margin. The neoplastic epithelioid cells were positive for clusterin and D2-40 (Fig. 2) and negative for CD163 immunohistochemical stains. CD163 immunostain highlighted dispersed histiocytoid cells. The neoplastic epithelioid cells were also negative for MNF116, desmin, SMA, caldesmon, S100, SOX10, CD31, ERG, SATB2, CD21, DOG1, MUC4 and H3K36M immunohistochemical stains (not shown). Nuclear staining for H3K27Me3 was retained. The final diagnosis was a hyalinised TGCT, favour localised type. This case was also reviewed by a pathologist with expertise in soft tissue tumours who agreed with the diagnosis (see acknowledgement below). At 12 days post-operation, the wound had healed and sutures were removed. The patient recovered well and remains on follow-up.

TGCTs are known to have varying degrees of stromal collagen deposition, however, to our knowledge, this is the first case report of TGCT with extensive stromal hyalinisation. The diagnosis was clinched by first recognising the characteristic epithelioid cells on morphology, even though there were no osteoclast-type giant cells present and confirming their synoviocyte lineage through strong and diffuse expression of clusterin and D2-40 on immunohistochemistry. The presence of extensive stromal hyalinisation in TGCT may pose a diagnostic challenge as it may mimic other tumours with prominent fibrosis or osteoid deposition. Differential diagnoses include hyalinising deep fibrous histiocytoma, chondroblastoma, sclerosing epithelioid fibrosarcoma and osteosarcoma.

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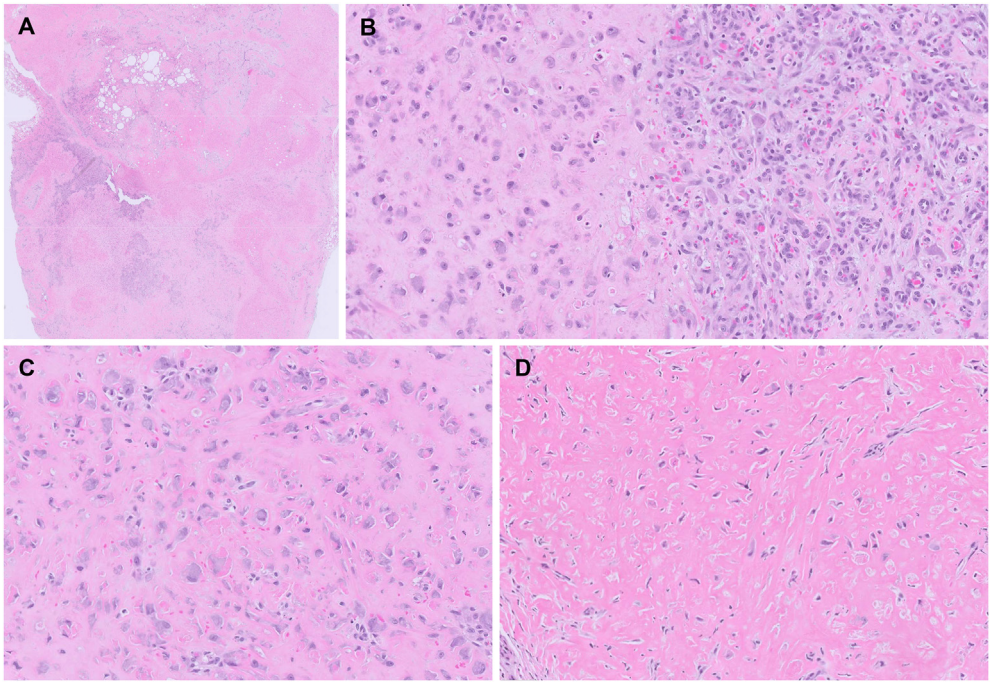

Fig. 1 (A) Low magnification histological view of excised mass from the right calf demonstrating a subcutaneous lesion composed of vaguely nodular areas with prominent hyalinised stroma separated by more cellular areas of reactive fibroblastic proliferation and capillary formation (H&E). (B) Higher magnification view showing hyalinised areas with adjacent area of reactive capillary formation and fibroblastic proliferation (H&E). (C) Hyalinised areas containing scattered neoplastic epithelioid cells (H&E). (D) Some areas of dense hyalinised stroma mimicking osteoid matrix (H&E).

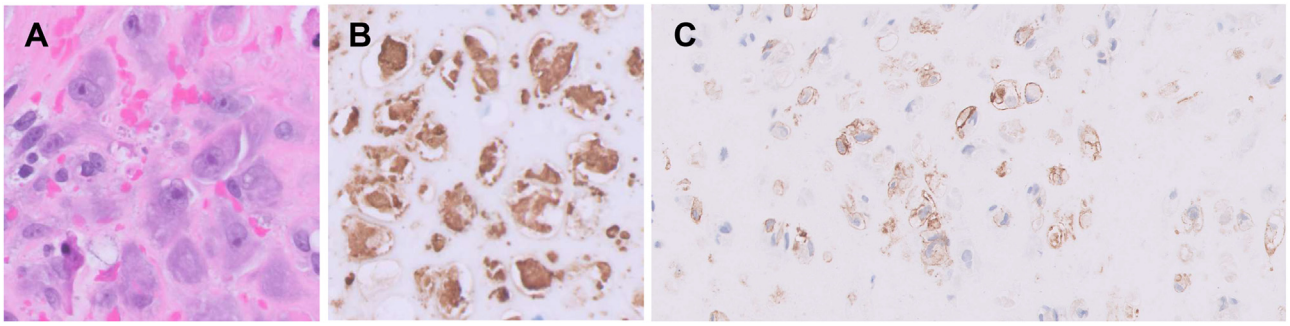

Fig. 2 (A) High magnification histological view of neoplastic epithelioid cells demonstrating dense eosinophilic cytoplasm, eccentrically-placed nuclei and prominent nucleoli (H&E) and positivity for (B) clusterin and (C) D2-40 immunohistochemical stains.

Deep fibrous histiocytoma (DFH) is a dermatofibroma that arises in the subcutaneous and deep soft tissues of the extremities and head and neck. Histologically, DFH is composed of a storiform pattern of monomorphic spindle cells with vesicular nuclei and branching staghorn-like vessels surrounded by a fibrous pseudocapsule. Often, there is prominent stromal hyalinisation and occasionally foamy histiocytes and osteoclast-like giant cells. Compared with TGCT, DFH lacks the sheets of large epithelioid and histiocytoid cells. In addition, the neoplastic cells in DFH are positive for CD34 in almost 40% of cases.

Chondroblastoma is a primary bone tumour that most commonly occurs in the epiphysis of long bones such as the tibia, femur and humerus and rarely in the bones of the hands and feet. Microscopically, it is composed of sheets of polygonal chondroblasts with eosinophilic cytoplasm, central grooved nuclei and delicate pericellular chicken-wire calcification. The matrix can be eosinophilic or chondroid with areas of osteoclast-like giant cells and haemosiderin deposition. Neoplastic cells are positive for S100, DOG1 and SOX9 immunostains. Up to 95% of chondroblastomas demonstrate a K36M mutation in either the *H3F3A* or *H3F3B* gene which can be confirmed by immunohistochemical staining. This mutant protein is absent in TGCT.

Sclerosing epithelioid fibrosarcoma (SEF) is a malignant neoplasm that arises most often in the deep soft tissues of the extremities, limb girdle, trunk and head and neck in adults. Histologically, lobules of monomorphic epithelioid cells with clear cytoplasm arranged in cords are present within a hyalinised sclerotic stroma. The margins typically infiltrate into adjacent muscle and adipose tissue. Immunohistochemically, SEFs show strong diffuse cytoplasmic positivity for MUC4 and are negative for cytokeratin. SEFs harbour multiple chromosomal rearrangements, most commonly the *EWSR1*::*CREB3L1* fusion. In contrast, TGCTs are negative for MUC4 and show the *COL6A3*::*CSF1* fusion.

Osteosarcoma is a high grade sarcoma of bone that has a bimodal age distribution and most commonly arises in the intramedullary metaphyseal regions of long bones of the extremities such as the femur, tibia and humerus. Histologically,

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sheets of pleomorphic spindle cells in a background of malignant osteoid deposition lacking osteoblastic rimming, is characteristic. Stromal hyalinisation in a TGCT may mimic the osteoid deposition seen in osteosarcoma (as seen in our case), however, the lack of malignant features and absence of woven bone formation favour the former.

The standard treatment for TGCTs is complete local excision. This is generally curative for L-TGCTs which exhibit a low recurrence rate of 0−15%.[1] D-TGCTs are locally aggressive and have a higher recurrence rate ranging from 21 to 50%.[1] Factors that contribute to recurrence include incomplete resection, presence of satellite lesions, incomplete encapsulation and intraosseous involvement.[3] Patients may require multiple surgical resections which can reduce their quality of life, increase morbidity and reduce function of the affected joint.[12] Adjuvant therapies are commonly incorporated in the management of TGCTs including radiotherapy and systemic therapy. Antagonists of the CSF1/CSF1R pathway including monoclonal antibodies such as emactuzumab and cabiralizumab and tyrosine kinase inhibitors (TKIs) such as imatinib and nilotinib have been disappointing.[12] However, in August 2019, the United States Food and Drug Administration (FDA) approved pexidartinib, an oral TKI with selective inhibition of CSF1R, for the treatment of symptomatic TGCT associated with severe morbidity or functional limitations not amenable to improvement with surgery.[12] In a randomised phase 3 trial (ENLIVEN), pexidartinib showed an overall response rate of 39% with a 14.8% complete and 24.6% partial response rate compared to the placebo.[13] The prognosis of TGCT with extensive hyalinisation is not known. In our case, the tumour extended to the resection margin and therefore close clinical follow-up is recommended.

Compliance with ethical standards: This study was conducted in accordance with guidelines from the Centralised Institutional Review Board of SingHealth. Written consent was obtained from the patient for publication of this case report.

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