Title

Tenosynovial Giant Cell Tumor, Localized Type With Extensive Chondroid Metaplasia: A Case Report With Immunohistochemical and Molecular Genetic Analysis

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Tenosynovial Giant Cell Tumor, Localized Type With Extensive Chondroid Metaplasia: A Case Report With Immunohistochemical and Molecular Genetic Analysis

Abstract

Tenosynovial giant cell tumor (TSGCT) of localized type is a common disease occurring mostly in the hands. Diagnosis of this tumor is relatively easy to render with H&E-stained sections as compared to that of TSGCT of diffuse type. However, very rare cases with chondroid metaplasia which has recently been reported mainly in diffuse type can make pathological differentiation from soft tissue cartilaginous tumors extremely difficult. The authors present the second reported case of TSGCT of localized type showing extensive chondroid metaplasia. Pathological interpretation was difficult without utilizing immunohistochemistry and fluorescent in situ hybridization. One must be careful not to misdiagnose this lesion as cartilaginous tumors of soft tissue and we suspect at least some chondroblastoma-like chondroma could be reclassified as TSGCT of localized type with extensive chondroid metaplasia. Morphological, immunohistochemical and molecular genetic characteristics are presented and discussed.

Keywords

Tenosynovial giant cell tumor, localized type, chondroid metaplasia, clusterin, *COL6A3-CSF1* fusion gene

Introduction

TSGCT arises from the synovium of joints. The tumor is divided according to its growth pattern into localized and diffuse types.[1] In contrast to the diffuse type (synonym: pigmented villonodular synovitis, PVNS), most of TSGCTs of the localized type (synonym: nodular tenosynovitis) occur in the hands, and they are relatively easy to diagnose for experienced pathologists. Histological examination shows a well circumscribed lobulated tumor composed of small histiocytoid cells and larger mononuclear cells intermingled with osteoclast-like multinucleated giant cells. Foamy histiocytes and siderophages are often present. However, it has recently been noted that TSGCTs may exhibit chondroid metaplasia and, when extensive, may cause difficulty in differentiating TSGCT from chondroid tumors including chondroblastoma-like chondroma and chondrosarcoma. Nineteen of the 20 reported cases of TSGCT with extensive chondroid metaplasia were of the diffuse type, preferentially involving the temporomandibular joints.[2-8] Only a single case of localized TSGCT with chondroid metaplasia involving the wrist has been reported.[9] Recently, immunohistochemistry (IHC) with clusterin has been found to be useful in the diagnosis of TSGCT.[10] In addition, approximately 60% of TSGCT have a unique *COL6A3-CSF1* fusion gene resulting from a t(1;2)(p13;q37) rearrangement [11,12]

We present a case of TSGCT of localized type showing extensive chondroid metaplasia. The histological features were reminiscent of cartilaginous tumors, rendering it virtually impossible to differentiate especially from chondroblastoma-like chondroma solely on the basis of H&E-stained sections. IHC and molecular genetic studies were employed to successfully aid in the differential diagnosis.

Case Report

Clinical Findings

A 72-year-old man presented with a tumor of his left hand. He first noticed the lesion 7 years prior, with a gradual increase in size since its onset. Physical examination revealed a well circumscribed subcutaneous tumor on the dorsum of his left hand. His past medical history included hypertension and coronary artery disease and stricture status post stent replacements, and abdominal aortic aneurysm. There was no history of antecedent trauma.

Computed tomography scan revealed a coarsely calcified tumor located in the subcutaneous tissue of the dorsal side of the left fifth metacarpal (Figure 1A and B). Radiographically, the tumor measured approximately 3cm in maximum diameter. The patient underwent simple local excision. The tumor was slightly adherent to the tendon, but was clearly

separated from the bone. There was no loss of function of his left 5th digit or hand.

Gross Pathology

Grossly, the excised specimen consisted of a well circumscribed tumor, which was about 2.5cm in maximum diameter. The cut surface was whitish in appearance. No necrosis was observed (Figure 2A and B).

Histopathology

On microscopic examination, the tumor showed a vaguely lobular pattern of growth on low power view. The tumor was attached to the densely collagenous tendinous tissue, and contained compressed cleft-like spaces. The stroma of the tumor lobules was strikingly chondroid in appearance (Figure 3A). With high power examination, the lobules with chondroid stroma were surrounded by large mononuclear cells, osteoclastic multinucleated giant cells and small histiocytoid cells. Their nuclei were bland in appearance (Figure 3B). The large mononuclear cells were scattered or clustered in interlobular spaces. They contained eosinophilic cytoplasm and eccentric nuclei, the features similar to chondroblasts (Figure 3C). The central area of each lobule also had scattered mononuclear cells. Some of these cells were located in lacunae with abundant myxoid cartilaginous stroma resembling mature hyaline cartilage, while other cells were less mature and spindled in shape. Their nuclei were mildly to moderately atypical and irregular in size and shape, but mitoses were not observed (Figure 3D). The stroma was stained positively with alcian-blue (data not shown) and exhibited metachromasia with toluidine-blue (Figure 3E). There were fibrosis and inflammatory infiltration between the lobules, the latter consisting of lymphocytes, plasma cells, histiocytes and fibroblasts. Although foamy macrophages were not conspicuous, a Berlin-blue stain revealed hemosiderin-laden macrophages in the interlobular spaces (Figure 3F). In some areas, intercellular fine calcification (Figure 3G) was conspicuous, but in other parts, the calcification was coarse (Figure 3H). Ossification with marrow spaces was present partially surrounding the chondroid lobules (Figure 3G).

Immunohistochemistry

Immunohistochemical staining was performed using the Ventana BenchMark ULTRA immunostainer (Ventana Medical Systems, USA) or BOND-III immunostainer (Leica Biosystems, Germany). All IHC procedures were conducted according to antibody and immunostainer instrument manufacturers' instructions. The small histiocytoid cells and the

multinucleated giant cells at the periphery of cartilaginous lobules and interlobular spaces were positive for CD68 (Roche Diagnostics, mouse monoclonal, KP-1) and CD45 (Roche Diagnostics, mouse monoclonal, RP2/18), but the large mononuclear cells were negative for both of these markers (Figure 4A and B). The expression of CD163 (Novocastra, mouse monoclonal, 10D6) and desmin (Roche Diagnostics, mouse monoclonal, DE-R-11) was not observed in either the mononuclear large cells or the multinucleated giant cells (Figure 4C). Most of the cells showing chondroid metaplasia at the center of the lobules were positive for podoplanin (Roche Diagnostics, mouse monoclonal, D2-40) (Figure 4D) and S-100 protein (Roche Diagnostics, rabbit polyclonal) (Figure 4E), but negative for CD45, CD68, CD163 and desmin. Some of the large mononuclear cells were also positive for podoplanin and S-100 protein. Clusterin (Biovender Laboratory Medicine, mouse monoclonal, Hs-3) which has recently been regarded as an excellent marker of TSGCT[10] was positive in the cytoplasm of the large mononuclear cells, but not in the small histiocytes or the multinucleated giant cells (Figure 4F). We also performed IHC with clusterin on a few typical cases of extraskeletal chondroma and chondroblastoma of bone, but all were negative (data not shown). However, unfortunately, it was unable to perform IHC with clusterin on a case of chondroblastoma-like chondroma, because we could not find such a case in our database. Ki-67 (Roche Diagnostics, rabbit monoclonal, 30-9) labeling index was very low (1-2%) in all of the cells comprising the lesion except in the infiltrating lymphocytes (data not shown).

Molecular Genetic Study

Molecular Genetic Study

We performed dual color interphase fluorescence in situ hybridization (FISH) analysis on formalin-fixed paraffin embedded (FFPE) sections using custom-made probes within the range of *CSF1* gene (1p11-13; clone RP11-759P, labeled in red) and the range of *COL6A3* gene (2 q35-37; clone RP11-66F3, labeled in green). FISH analysis showed overlapping yellow signals on tumor nuclei, indicating the presence of a *CSF1-COL6A3* fusion gene (Figure 5). The tumor cells harboring this fusion gene were in a fraction accounting for 3.9 to 13.1% of all tumor cells depending on the places examined.

Discussion

TSGCT of localized type has also been called by the name of giant cell tumor of tendon sheath or nodular tenosynovitis, and it is a relatively common tumor in the hands. Its histological features are so characteristic in most of the cases and the tumor so well circumscribed that pathological diagnosis is not difficult to render as compared to diffuse type (PVNS). There have been some reports of PVNS exhibiting chondroid metaplasia with nearly all of these reported cases involving temporomandibular joints.[2-8] Only a single case involving the wrist of TSGCT of localized type with chondroid metaplasia has been previously reported.[9] However, the latter report was mainly focused on the cytological features observed on fine needle aspiration. The present case is only the second case report of localized type of TSGCT with extensive chondroid metaplasia, and to the best of our knowledge, detailed histological features and immunohistochemical and molecular analyses have not been reported so far.

TSGCT of localized type with extensive chondroid metaplasia must be distinguished from cartilaginous tumors. Extraskeletal chondroma occurs mainly in the hands and feet, and they may be attached to the tendon or tendon sheath.[13] If a core biopsy is taken mainly from the central portion of TSGCT of localized type with extensive chondroid metaplasia, differentiation from chondroma might be impossible on H&E section alone. Even an excised tumor could be problematic in arriving at an accurate diagnosis, because in about 15% of cases, chondromas contain epithelioid cells and multinucleated giant cells at the tumor margin and along the interlobular spaces reminiscent of TSGCT. [13] Moreover, TSGCT of localized type is normally lobulated and as seen in the present case it can exhibit mature and immature cartilaginous features with calcification reminiscent of chondroma. Furthermore, in our case, the cells in the chondroid metaplastic areas were positive for S-100 protein and demonstrated mild to moderate nuclear atypia. In fact, our first impression of our present case was that of chondroblastoma-like chondroma, because eosinophilic large mononuclear cells in our case greatly resembled chondroblasts or chondroblast-like cells seen in cartilaginous tumors. Chondroblastoma-like chondroma was first reported by Isayama et al.[14] It is regarded to be a very rare tumor with only 13 cases reported[15] and has not been widely accepted as an independent disease entity. Fortunately, the prognosis of TSGCT of localized type and chondroma do not differ significantly.[16,17] However, in the future, it will be necessary to study how chondroid metaplasia and chondroblastoma-like changes affect the recurrence rate of TSGCT and chondroma of soft part, respectively. Clusterin is a useful marker for the diagnosis of TSGCT,[10] and we believe IHC with clusterin antibody should be employed in difficult cases like ours for differentiation from true cartilaginous tumors. The large mononuclear cells in our case showed diffuse positivity with clusterin. Also, recent cytogenetic studies have elucidated that TSGCT, either localized or diffuse type, shows one or a few chromosomal rearrangements

involving the short arm of chromosome 1. The most prevalent rearrangement is t(1;2)(p11-13;q35-37), resulting in a *COL6A3-CSF1* fusion gene,[11,12] which was also detected by FISH analysis in the present case. This fusion gene has not been reported to be present in cartilaginous tumors.[18,19] Although only a low percentage (3.9 to 13.1%) of cells showed fusion signals in our case, the result is almost identical to that of the previous report.[11] We suspect that at least some chondromas, especially chondroblastoma-like chondromas of soft part could potentially be reclassified as TSGCT with extensive chondroid metaplasia, if IHC with clusterin and FISH analysis for *COL6A3-CSF1* fusion gene were to be performed.

The extraskeletal chondroblastoma is most rare, but should be considered in the differential diagnosis. Since the first case reported by Kingsley et al. in 1971,[20] only five cases have been documented, the latest case even exhibiting malignant behavior.[21] The microscopic findings in these extraosseous cases showed very similar histology to their skeletal counterparts. The calcifications in our case were a bit different from the typical "chicken-wire" calcifications of chondroblastoma. Moreover, the number of large mononuclear cells were far fewer than those of the reported chondroblastoma cases.

Chondromyxoid fibroma is an uncommon benign cartilaginous tumor that involves the metaphyses of long bones. Two reports of extremely rare chondromyxoid fibroma of soft tissue have been published. [22,23] However, both were focused on radiographic or sonographic findings, and the histological findings were not elucidated. It might not be necessary to include chondromyxoid fibroma in differential diagnosis at this point, if the tumor is obviously originated from soft tissue without connection to bone.

Regarding differentiation from malignant tumors, the necessity to distinguish extraskeletal myxoid chondrosarcoma is unlikely, since it is extremely rare in the hands and the histological features are very unique. It is composed of cords of atypical cells in an abundant myxoid stroma. Differentiated cartilage cells within lacunae are rare.[24,25] On the other hand, when only the chondroid metaplastic part of TSGCT is sampled in a small biopsy specimen, mild to moderately atypical chondroid cells may be seen, as in our present case and may confuse inexperienced pathologists in excluding mesenchymal chondrosarcoma, although it is also extremely rare in the hands.[26] In this situation, IHC with clusterin and/or FISH analysis may be of help. If an excised tumor is examined, mesenchymal chondrosarcoma can be readily excluded, because it exhibits proliferation of undifferentiated cells around relatively well differentiated cartilaginous islands, which would not be seen in TSGCT of localized type with chondroid metaplasia.

In summary, we present a very rare case of TSGCT of localized type with extensive chondroid metaplasia, the morphological findings of which were indistinguishable from those of chondroblastoma-like chondroma. It is necessary to be aware that the localized type of TSGCT, and not only diffuse type may exhibit extensive chondroid features which can render

it very difficult to differentiate pathologically from other cartilaginous tumors. IHC and/or FISH analysis should be recommended when a benign localized soft tissue tumor shows mononuclear large cells and osteoclastic multinucleated giant cells around cartilaginous islands. We suspect there is a possibility that at least some soft tissue chondromas of the hands are reclassified as TSGCT with extensive chondroid metaplasia. An accumulation of more cases should be performed.

Declaration of Conflicting Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figure legends

Figure 1.

Noncontrast CT of the left hand. (A) Coronary view; (B) Axial view. A well circumscribed subcutaneous tumor with coarse calcification is seen on the dorsal side of the fifth metacarpal bone.

Figure 2.

Cut surface of the tumor is whitish, surrounded by adipose tissue.

Figure 3.

Light microscopic findings of the tumor with H&E stain and conventional histochemistry. (A) Cross sectional view showing a lobulated tumor with extensive chondroid metaplasia dotted by calcification, reminiscent of chondroma. Dense collagenous tissue of the tendon in conjunction of the tumor is seen in the upper left part of the specimen. (B) Large mononuclear cells intermingled with multinucleated giant cells are seen at the periphery of metaplastic chondroid lobules. Smaller histiocytoid cells, lymphocytes, plasma cells and fibroblasts are also present in the interlobular spaces, x200. (C) An aggregate of large mononuclear cells with eosinophilic cytoplasm and eccentric nucleus, x400 (D) The central area of the lobules composed of mature and somewhat immature chondrocytes in a myxoid background, x200 (E) Myxoid background of the lobules showing metachromasia with toluidine-blue (pH7.0), x100. (F) Berlin-blue stain revealing hemosiderin deposition. (G) Ossification with bone marrow space and fine calcification surrounding chondroid cells, x100. (H) Coarsely calcified area, x100.

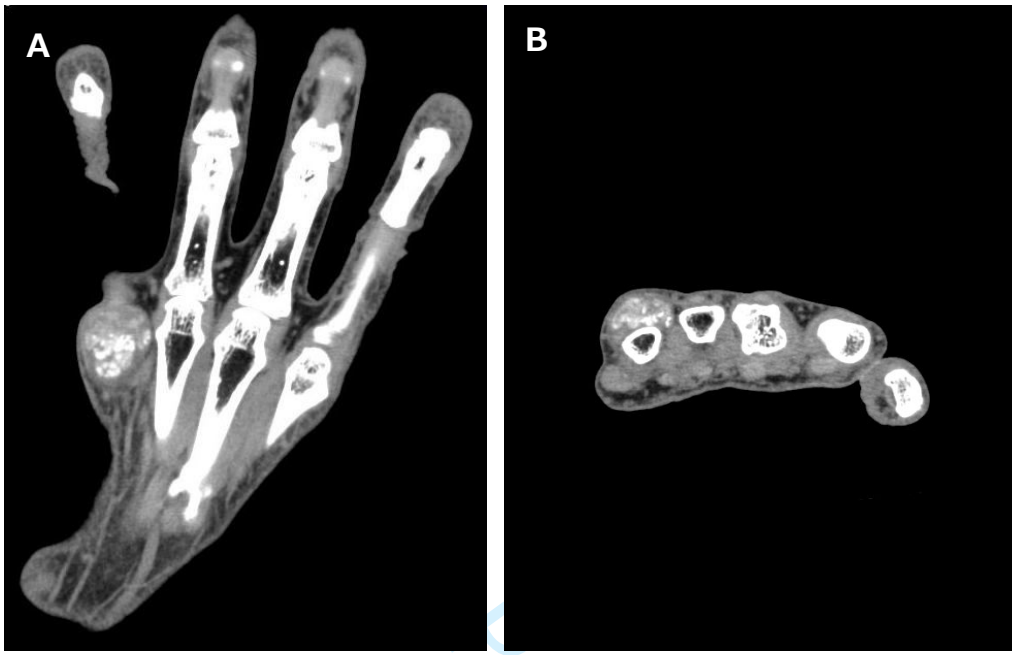
Figure 4.

Immunohistochemical analysis. (A) CD68, x200. (B) CD45, x200. (C) CD163, x200. (D) Podoplanin, x400. (E) S-100, x400. (F) Clusterin, x400.

Figure 5.

FISH analysis using custom-made probes for *CSF1* (red signals) and *COL6A3* (green signals) genes showed overlapping yellow signals (arrow), confirming the existence of a CSF1-COL6A3 fusion gene.

Figure 1.



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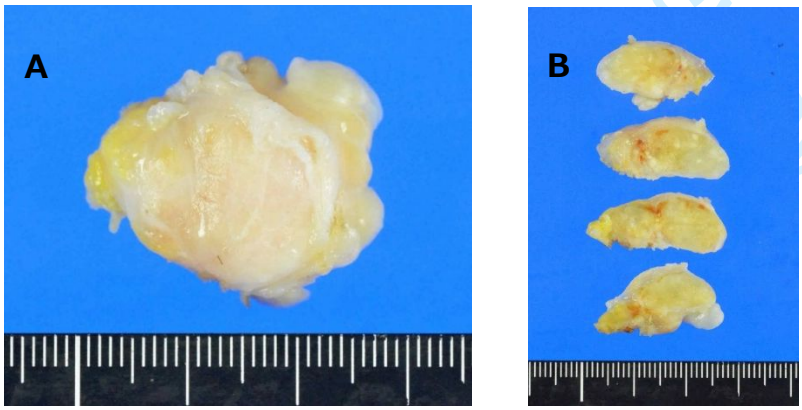

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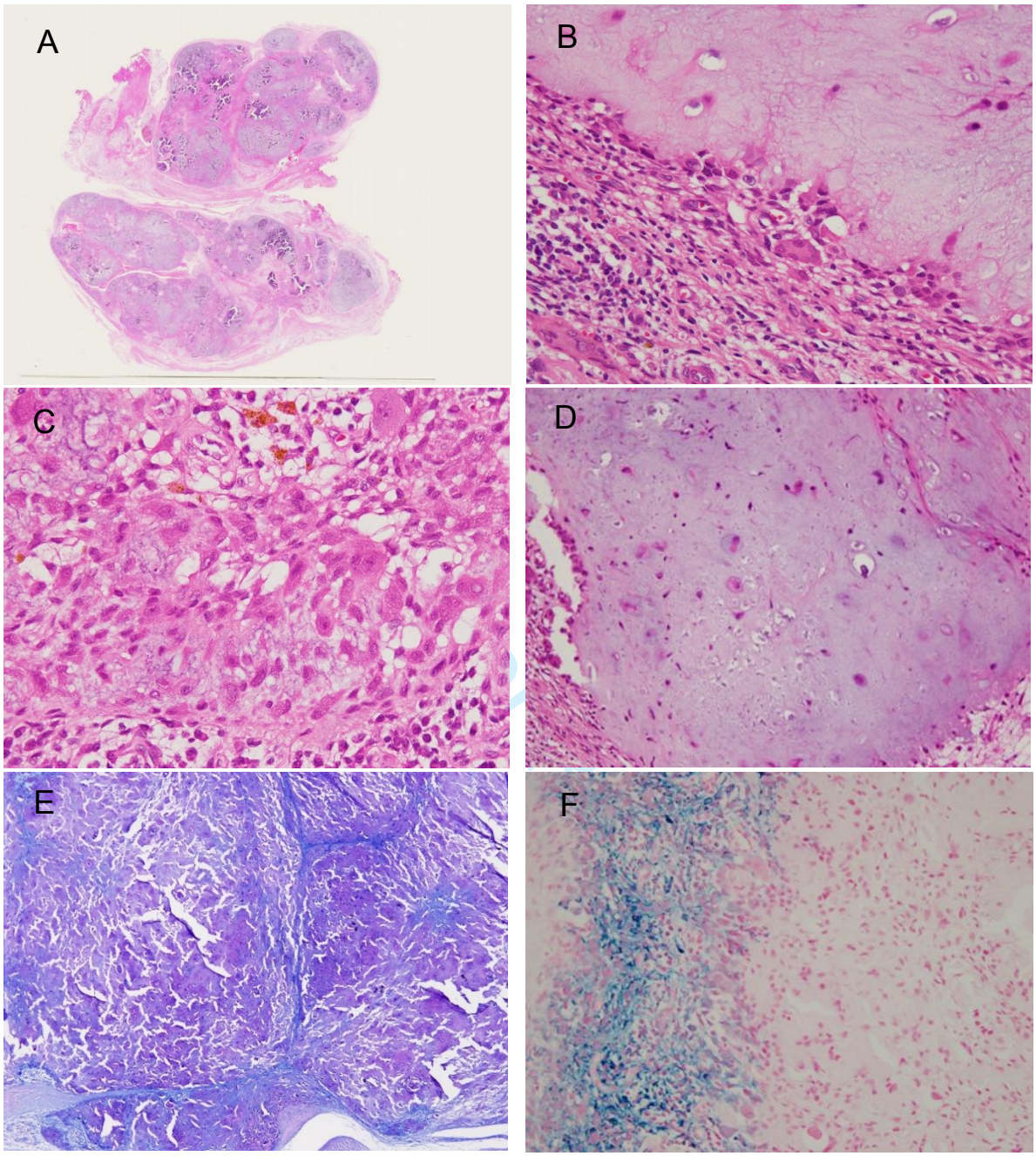

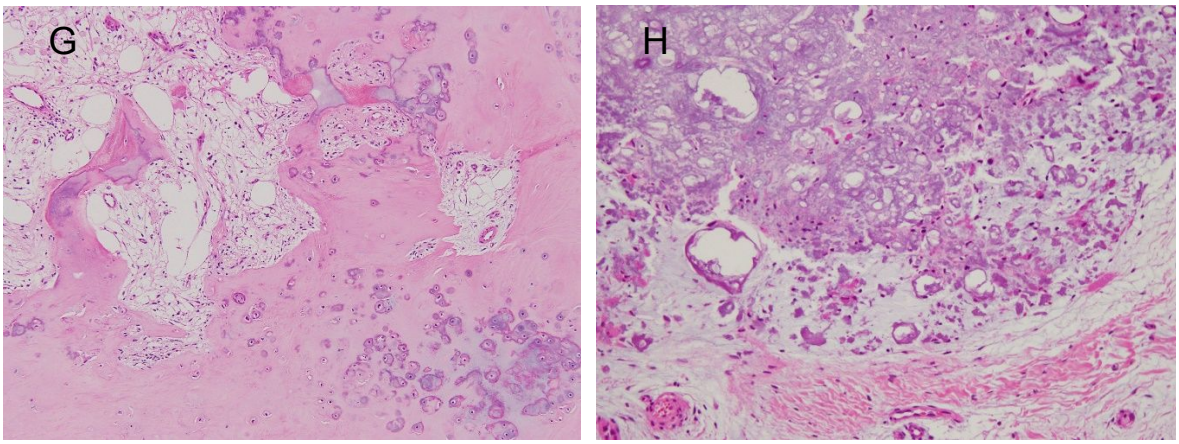

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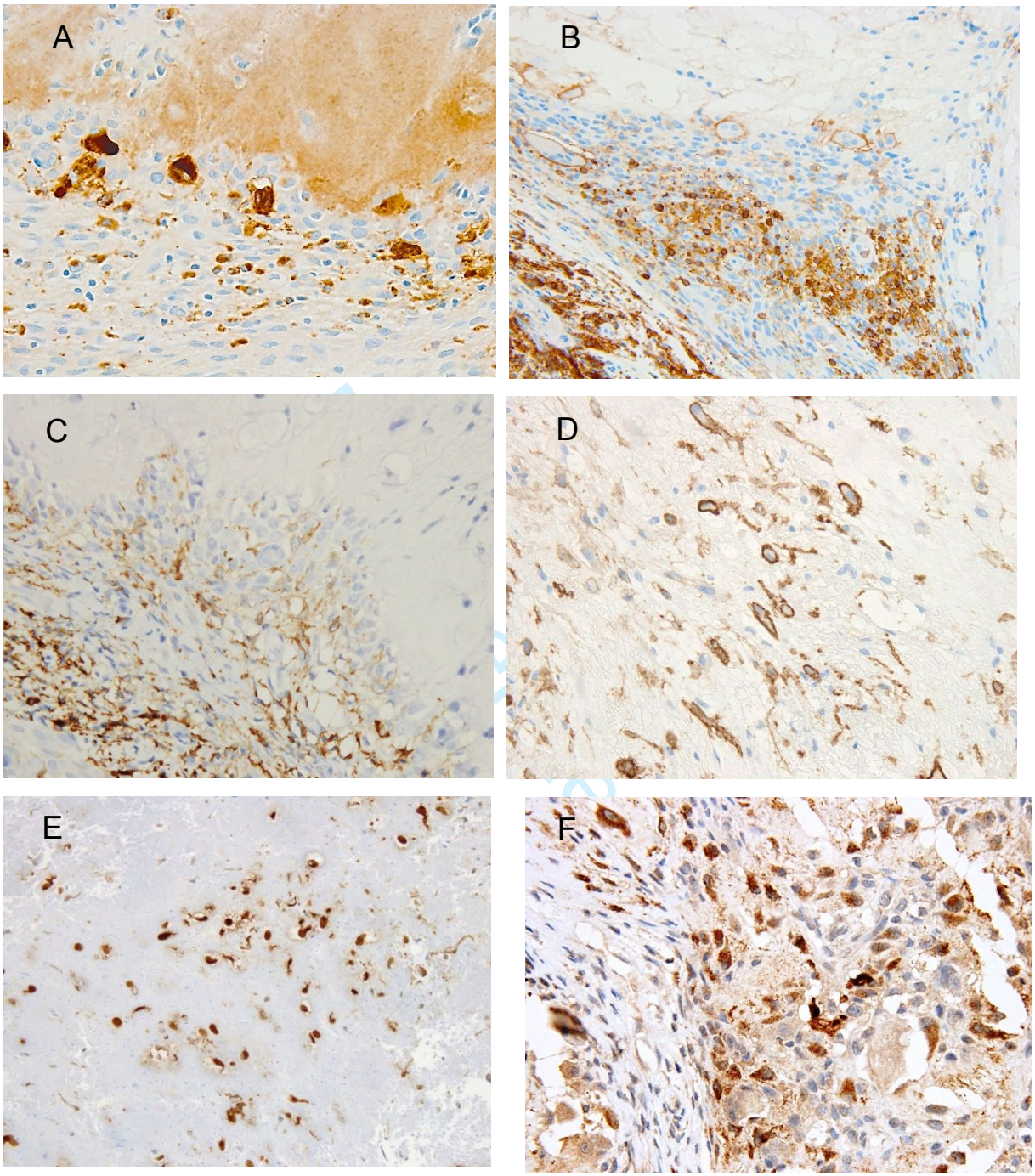

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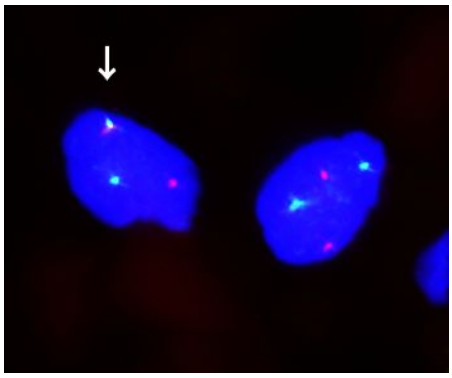

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