Xanthogranulomatous Epithelial Tumor: A Case Report with One-Year Follow-Up

Muna Abuhejleh[1], Ahmed ElSayed[1], Renan Adam [1], Asmaa Mohamed[1], and Adham Ammar[1]

[1]Hamad Medical Corporation

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Muna AbuHejleh[1], Ahmed Mounir ElSayed[2], Renan Elsadeg Ibrahem[3], Asmaa Elhassan Mohamed[4], Adham Ammar[1]

1Department of Laboratory Medicine and Pathology, Hamad Medical Corporation, Doha, Qatar; Mabuhejleh@hamad.qa, Aammar1@hamad.qa

2Department of Orthopedics Surgery, Hamad Medical Corporation Doha Qatar; Aelsayed7@hamad.qa

3Department of Clinical Imaging, Hamad Medical Corporation, Doha Qatar; Radam1@hamad.qa

4Oncology Hematology Department, National Center for Cancer Care and Research (NCCCR), Hamad Medical Corporation, Doha, Qatar; Amohamed2@hamad.qa

***Corresponding author:**

Muna AbuHejleh, PO BOX 3050,

Department of Laboratory Medicine and

Pathology, Hamad Medical Corporation,

Doha, Qatar.

Email: Mabuhejleh@hamad.qa

Key Clinical Message

Xanthogranulomatous epithelial tumor (XGET) is a rare soft tissue and bone neoplasm with distinct immunophenotypic and molecular features. The banal histomorphological characteristics of this lesion fail to foreshadow its potentially aggressive clinical behavior. The prognostic and therapeutic significance is not sufficiently explored due to the rarity of this entity.

Case History/examination:

A 29-year-old male with no previous medical or surgical history presented with right hip pain for 1-year duration. Physical examination showed right anterior hip joint tenderness. Imaging showed an ill-defined expansile lytic lesion of the right acetabulum centered in the posterior column and extends to involve the lower margin of the iliac bone causing complete osseous destruction (**Figures 1-3**). There is involvement of the acetabular articular surface. The lesion demonstrated locally aggressive radiological features and was suspicious of a malignant neoplasm. Whole-body FDG PET/CT scan demonstrated intensely increased

tracer uptake (SUV max 12) at the site of the acetabular/ iliac lesion highly suggestive of malignancy. Otherwise, no abnormal uptake to suggest local or distant metastasis (**Figures 4**).

Methods (Differential diagnosis, investigations and treatment):

A needle core biopsy was taken from the lesion. Microscopic examination showed a prominent proliferation of xanthomatous histiocytes and smaller fibrohistiocytic cells. There are also isolated epithelioid cells with moderate nuclear atypia. Few osteoclasts giant cells were also noted. No marked pleomorphism, necrosis, or atypical mitosis was identified. No features of an overt inflammatory process nor other mesenchymal components (**Figure 5a**).

Immunohistochemical studies showed focal positive keratin expression in the epithelioid cells. (**Figure 5b**). However, cells were negative for low molecular weight keratins such as CK7, CK8/18, and CK CAM5.2. Xanthomatous cells showed diffuse positivity for CD68 and factor XIIIa. While smooth muscle, vascular, and neural differentiation markers were negative. INI-1 (SMARCB1) immunohistochemistry retained its nuclear positivity.

The initial suggested morphological differential diagnoses were fibrohistiocytic lesion of bone, non-ossifying fibroma, and exuberant reaction to adjacent neoplasm. However, focal keratin positivity and the absence of other inflammatory features ruled out those possibilities. Thus, Xanthogranulomatous Epithelial Tumor (XGET) emerged as a working diagnosis. Given its rarity and scant literature, the case underwent central review at a referral center, which concurred with our diagnosis. Our case underwent a sarcoma-targeted gene fusion panel analysis, yet no fusion was identified.

The patient initiated Denosumab therapy as part of a trial to mitigate the need for extensive surgery. The patient is currently under regular follow-up to monitor the efficacy and safety of this novel treatment approach.

Conclusion and Results (Outcome and follow-up):

Our patient started Denosumab therapy, by which the size of the acetabular/iliac expansile mass lesion remains stable and the after 7 months of therapy, the follow-up PET/CT shows a significant reduction of the SUV max from 12 to 6.7. Clinically, the patient reported reduced pain with good clinical response. Hence, he continued Denosumab for another six months, anticipating potential surgery. One year after therapy, the patient only experienced pain upon bending, long walks, and running. MRI showed stable lesion size with slight internal changes. A recent PET/CT scan demonstrated a stable lytic lesion with mild improvement. Currently, the patient resumed his job and reported no pain or other complaints. He continued Denosumab therapy with regular follow-ups.

Discussion:

XGET is an unusual soft tissue and bone neoplasm with controversial and nonspecific radiological and histopathological features. A comprehensive literature search was conducted to identify previously reported cases of XGET. A total of 8 cases were identified, in a wide range of ages and with slight female predominance. The most common sites of involvement were soft tissue of the extremities, followed by bone. Clinical presentation varied from painless mass to localized pain or swelling. The tumor was first described by Fritchie et al. in 2020 as an unusual mesenchymal neoplasm with indolent biological behavior.[1] Six cases were identified arising in five females and one male with a median age of 21 years {range:16-62}. Four cases arose in soft tissue in the lower extremities and trunk. Two cases are presented in bone. In 2022, the seventh case was described by Dehner et al., a 37-year-old female who presented with a calf mass.[2] In a recent case report published by Svantesson et al. in 2023, they described a new case in a 66-year-old female who presented with a mass in her left thigh[4](**Table 1**).

The pathogenesis of XGET remains uncertain and few theories regarding the cellular origin have been proposed. In 2021, Agaimy et al. hypothesized that the presence of HMGA2-NCOR2 gene fusion is potentially specific to a rare low-grade entity known as “Keratin positive giant cell tumor of soft tissue (KPGCT)”. To

test the hypothesis, the author analyzed 15 cases of giant cell rich tumor that arose in soft tissue. Only keratin-positive cases harbored the distinctive HMGA2-NCOR2 gene fusion. While keratin-negative giant cell tumors were negative for this gene fusion.[3] Since then, Dehner et al. studied the morphological, immunohistochemical, and molecular similarities between XGET and KPGCT. Both tumors were believed to be morphological variants of a single entity. HMGA2-NCOR2 gene fusion was detected in both neoplasms. The shared clinical, molecular, and immunohistochemical features supported the author's theory.[2]

Histological findings were consistent across all reported cases of XGET, revealing sheets of foamy histiocytes accompanied by osteoclast and Touton-type giant cells. Additionally, mononuclear cells with bright eosinophilic cytoplasm were observed. While necrosis was reported in one case, no marked nuclear atypia or atypical mitoses were detected.[1,2,4]

Immunohistochemistry studies were conducted in all cases, yielding similar results. Cells exhibited at least focal positivity for keratin, CK7, and some displayed positivity for high molecular weight keratin. Additional immunohistochemistry studies, such as BRAF V600E and Histone H3G34W, were performed in some cases, all yielding negative results. Interestingly, MDM2 nuclear positivity by immunohistochemistry was observed focally in the eighth case, but no MDM2 gene amplification was detected by FISH analysis.

Molecular studies were performed in four cases. Case 1 displayed a PLEKHM1 mutation, which correlated with the patient's osteopetrosis diagnosis.1 In the seventh case, HMGA2-NCOR2 gene fusion was identified.[2] However, no gene fusions were detected in the remaining cases.

Radiological imaging studies were available for six cases (Table 2). Among soft tissue cases, the majority exhibited subcutaneous solid heterogeneous masses (cases 1, 5, and 7)[1,2] or well-defined soft tissue mass with a suspected focal invasion of cortical bone (case 8)[4]. In contrast, bone tumors demonstrated lytic lesions with sclerotic rims (Cases 3 and 6). No imaging studies were available for cases 2 and 4.1 No evidence of metastasis in the eight cases.[1,2,4]

To date, the management of XGET poses several challenges due to its rarity and lack of established treatment guidelines. The optimal management of XGET is yet to be established. While surgical resection remains the cornerstone of therapy, the potential morbidity associated with extensive surgery underscores the importance of exploring alternative modalities.

Various management approaches were undertaken in the previous reported cases. Six of the cases were treated by surgical excision (cases 1, 2, 4, 5, 7, and 8), one case was biopsied only (case 3) and one case was planned for excision (case 6). Cases that underwent complete surgical resection appear to be disease-free upon follow-up (follow-up range: 3-15 months).[1,2,4]

Here, we discuss the therapeutic approach involving Denosumab as an alternative to extensive surgery. Studies have explored the role of Denosumab, a monoclonal antibody targeting the RANK ligand, in the management of giant cell tumors of bone,5 which share histopathological similarities with XGET. Denosumab has demonstrated promising results in reducing tumor size and alleviating symptoms in giant cell tumors, raising interest in its potential utility in other neoplasms such as XGET. However, further studies are warranted to assess the long-term efficacy and safety of Denosumab in the management of XGET.

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Statement of Ethics: Written informed consent was obtained from the patient for the publication of his case.

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Mounir ElSayed, Dr Renan Elsadeg Ibrahem and Dr Asmaa Elhassan Mohamed, provided us with the clinical/radiological findings and follow up clinical findings.

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Figure legends

Figure 1. X-ray study shows an ill-defined expansile lesion of the right acetabulum.

Figure 2. CT images of the pelvis show an expansile lytic lesion of the posterior column of the right acetabulum with breaching of the medial and lateral cortices as well as the articular surface.

Figure 3. MRI axial images of the right hip joint. The lesion shows bland signal (isointense to muscles) on T1W images (A) and intermediate signal on STIR images (B). Mild diffuse enhancement seen in the post contrast images T1W FS (D) in reference to the pre contrast T1W FS (C).

Figure 4. FDG PET/CT shows intensely increased tracer uptake in the expansile right acetabular/iliac osseous lesion.

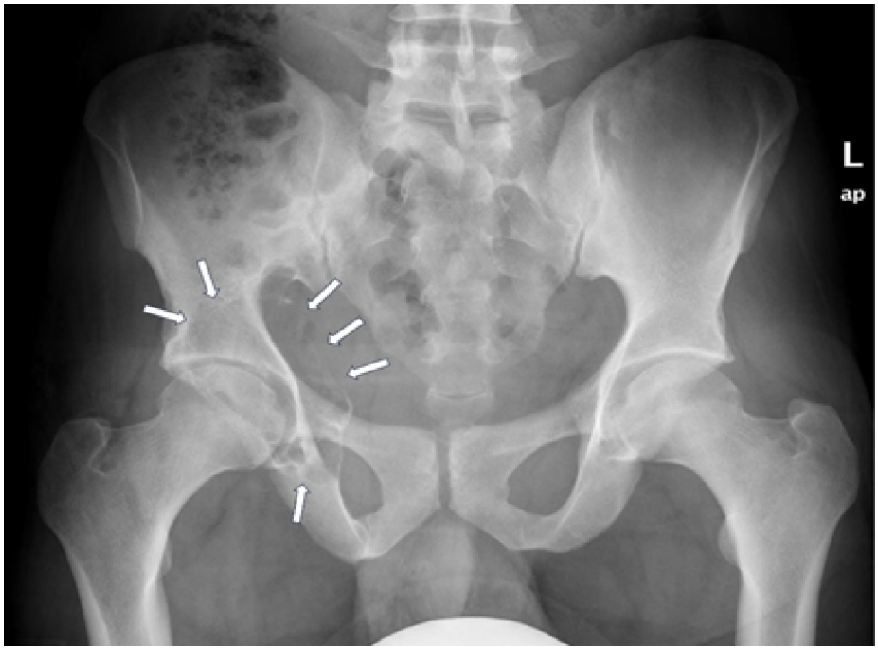
Figure 5a. Light microscopic examination reveals a tumor characterized by a proliferation of xanthomatous histiocytes with smaller, moderately atypical epithelioid cells. Additionally, a few osteoclast giant cells were noted (yellow arrows) (H&E stain, magnification x100, x400).

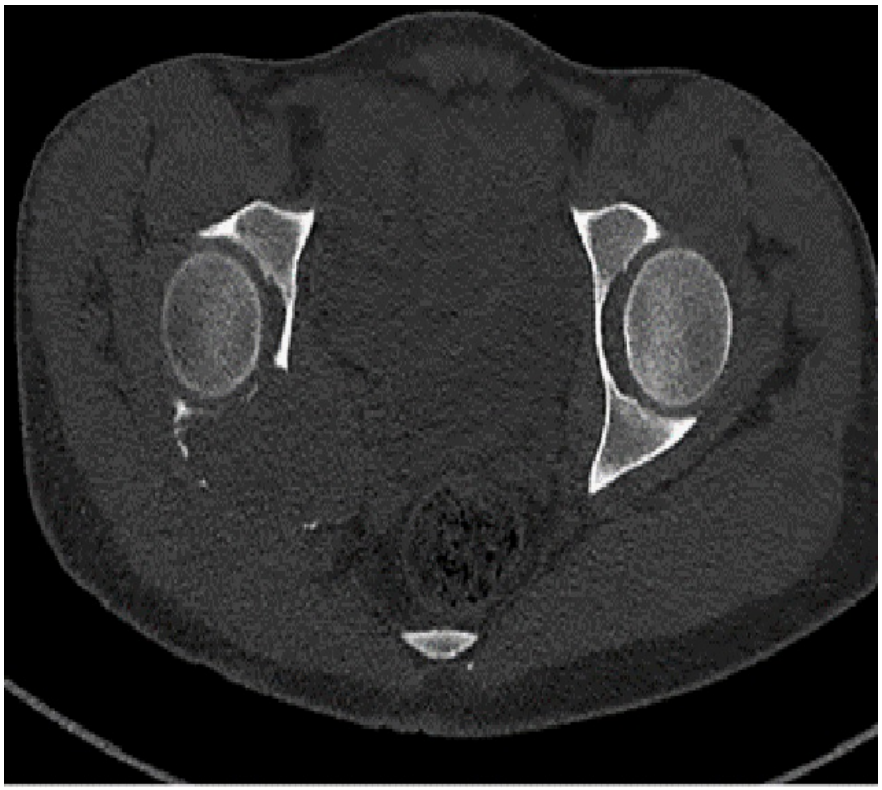
Figure 5b. Isolated epithelioid cells were highlighted by keratin immunohistochemistry (H&E stain, x400).

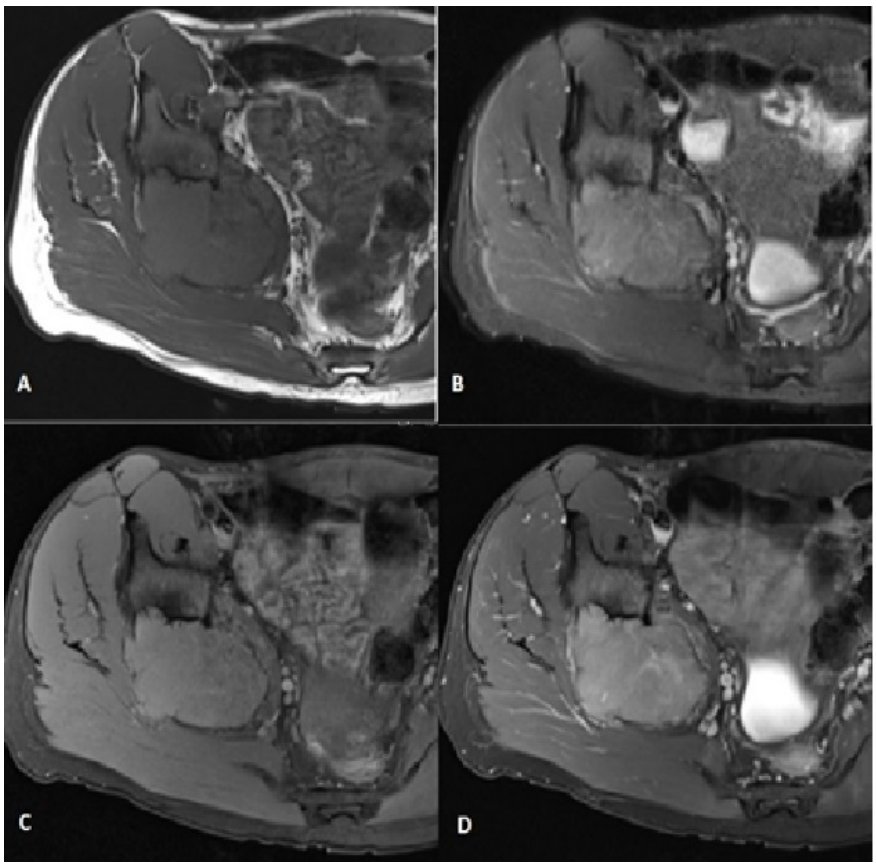
Table legends

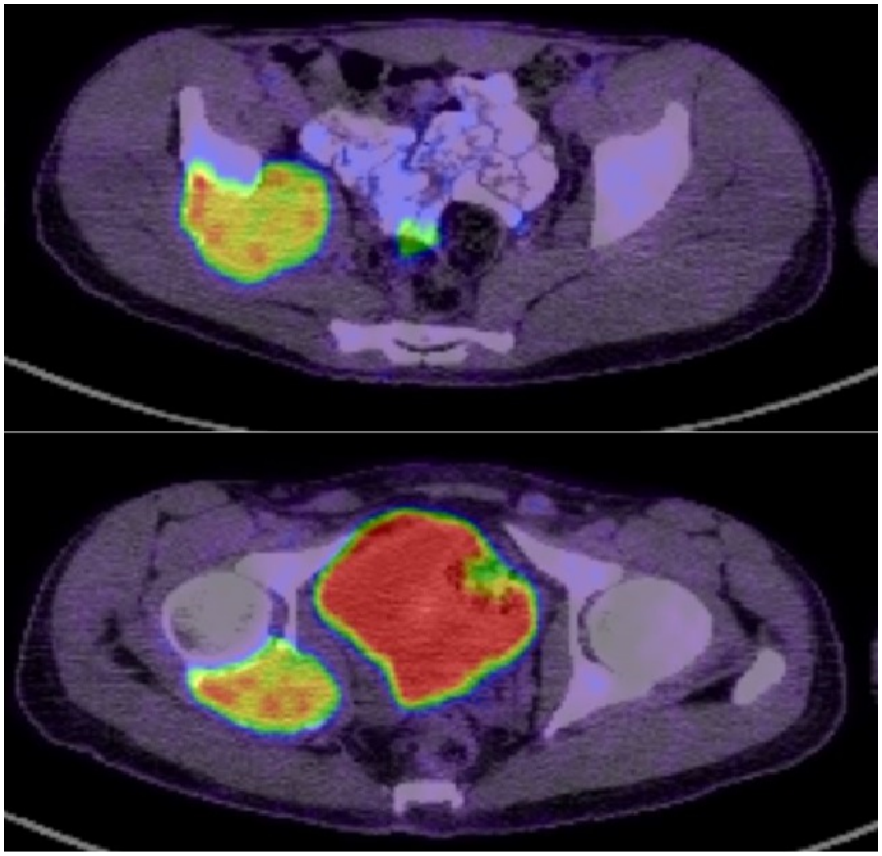
Table 1. Cases of Xanthogranulomatous epithelial tumor.

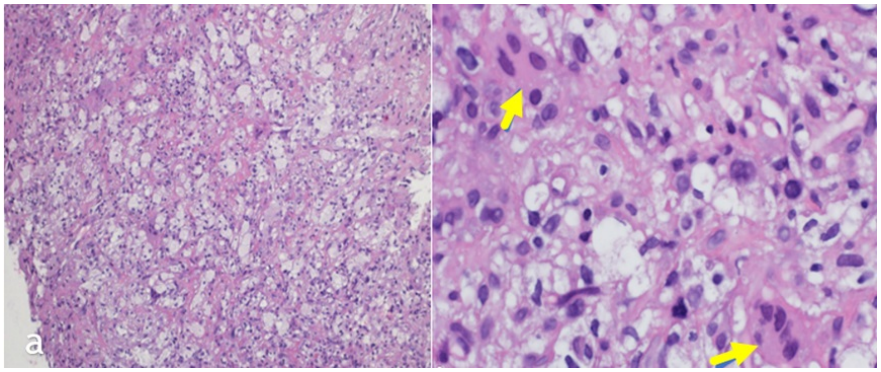
Table 2. Clinical features observed in reported cases of XGET.

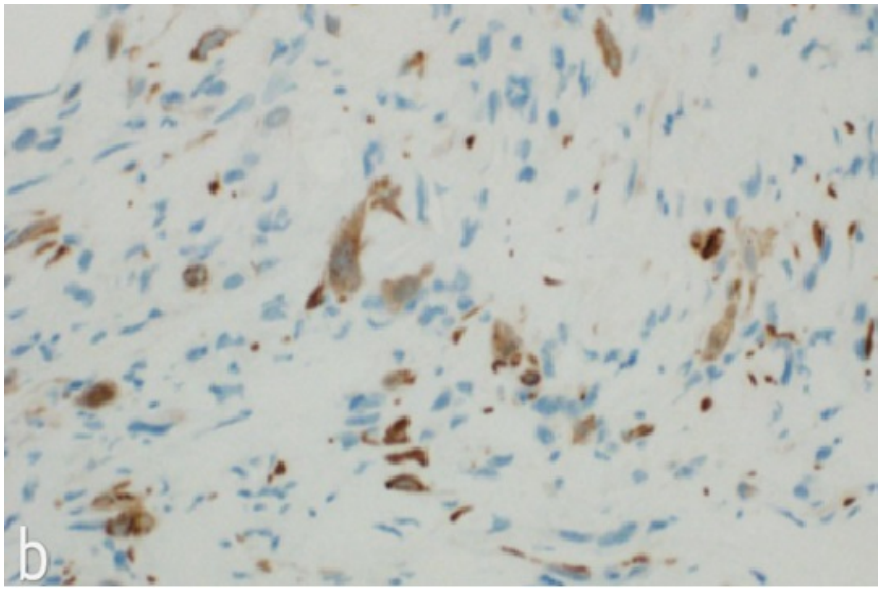












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