XANTHO-GRANULOMATOUS OSTEOMYELITIS OF STERNUM, RESEMBLING A TUMOR: FIRST REPORTED CASE
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Abstract:
Xantho-granulomatous inflammation is a rare type of chronic inflammation, when seen in the bones it is known as xanthogranulomatous osteomyelitis (XO). Here we present a rare case XO of the manubrium sterni, to best of our knowledge this is the first diagnosed. XO of the manubrium sterni mimics radiologically as tuberculosis and as eosinophilic granuloma. We have a 23 year old lady who presented with pain and swelling in the anterior chest, radiology was done and finally the lesion was biopsied. We accepted the patient as Xanthomatous Osteomyelitis and planned for excision of manubrium sterni, with a flap comprising of ribs and muscle advancements to cover the midline gap in the chest wall, that would have been created. Meanwhile she was put on a short course of antibiotics. It had been observed that the first open biopsy scar had exhibited a tendency for keloid formation. Hence, the risk of final surgery incision producing a disfiguring keloid was informed to the patient, which unfortunately led the patient deter surgery indefinitely, since she was to be married soon. We proposed a local injection of steroid into the lesion to minimize the inflammation. Under image intensifier we injected 40 mg of methyl prednisolone into the tumor. There was some tolerable discomfort the next day of injection that eventually subsided in 3 days. However, the biopsy came inconclusive second core needle biopsy came as XO. Since 1984 with the first case by Cozzutto et al, only 17 cases have been reported in the worldwide literature including us.

Introduction:
Xantho-granulomatous inflammation (XI) is a very rare variety of chronic inflammation, though usually witnessed in bladder, kidney, pancreas, fallopian tube, ovary, epididymis, testis, prostate and salivary glands (1) but when seen in bones, it is k/a Xanthogranulomatous osteomyelitis (XO). XO is characterized by the accumulation of foamy macrophages along with mononuclear cells in the tissue (2). It’s emergence in the brain, lungs, and bones is very rare (3). In bones it may present as an osteolytic lesion, with minimal or no periosteal reaction. The chronic course of the lesion resembles either tubercular affection or tumorous origin. Though C-T scan stands mandatory to define the osseous involvement of the lesion and MRI is compulsory to delineate its soft-tissue expansion, yet they are insufficient to conclusively dictate the final diagnosis. Histo-pathological evaluation coupled with immuno-histo chemistry, remain the mainstay for the final verdict. To the best of our knowledge, this is the first case of XO of manubrium sterni, to be ever reported in the English literature that had mimicked radiologically as tubercular, then as eosinophilic granuloma on simple histology, until IHC at last defined the final diagnosis of XO.

Case presentation:
This 23year old lady, presented to us with pain and swelling in front of upper chest, in and around manubrium sterni, with local signs of inflammation. Her blood parameters showed slight increase in ESR, CRP, alkaline phosphatase with normal serum calcium levels. She already had emperically taken three months anti-tubercular therapy, elsewhere, comprising
of isoniazid, rifampicin, pyrazinamide, and ethambutol, but in vain. There was no improvement whatsoever, with the anti-tubercular therapy. She underwent her first biopsy (open) elsewhere and then presented to us.

On presentation, her x-ray lateral view sternum showed an osteolytic lesion in the manubrium, with no cortical expansion. The AP x-ray was inconclusive. Her both CT scan and MRI, were more informative and detailed the osteolytic lesion in the manubrium. There was a frank breach in the anterior cortex, superiorly. And there was evidence of some tumor tissue outside the bone also. The overall tumor tissue appeared homogenous, without any cartilaginous or osseous images. There were no cavities or fluid visible in the tumor tissue. The posterior cortex was intact. Adjoining clavicle and ribs were clearly visualized as uninvolved.

The patient, after the failed trial of anti-tubercular therapy, then suspecting a neoplasm consulted a general onco-surgeon, who generously performed an open-biopsy at the upper end of the manubrium. The biopsy reported Inflamed dead parasitic cyst (Cysticercosis), with histiocytic granulomatous collection. Surprisingly, the slides on review, showed the lesion being an Eosinophilic Granuloma with large foamy histiocytes like cells, lymphocytes, plasma cells and eosinophils. The patient continued with analgesics and at this stage presented to us.

Since the first biopsy and both histological opinions were inconclusive, we decided for a second (Core-needle) biopsy. The second biopsy showed Xanthomatous osteomyelitis with accumulation of foamy histiocytes, and inflammatory cells. Specimen was further evaluated for IHC which showed: Vimentin: Positive, S 100: Positive & CD1a100: Negative.

We accepted the patient as Xanthomatous Osteomyelitis and planned for intoto excision of manubrium sterni, with a flap comprising of ribs and muscle advancements to cover the midline gap in the chest wall, that would have been created. Meanwhile she was put on a short course of antibiotics. It had been observed that the first open biopsy scar had exhibited a tendency for keloid formation. Hence, the risk of final surgery incision producing a disfiguring keloid was informed to the patient, which unfortunately led the patient deter surgery indefinitely, since she was to be married soon. We proposed a local injection of steroid into the lesion to minimize the inflammation. Under image intensifier we injected 40 mg of methyl prednisolone into the tumor. There was some tolerable discomfort the next day of injection that eventually subsided in 3 days. The patient reported back after 3 weeks, with almost total relief from local inflammation. There was no pain and erythema on the manubrium. The local tenderness was minimal and her full chest expansion became pain free. She has stopped all analgesics ever since. We wondered at the unexpected outcome and advised her a repeat CT scan and blood tests. Her total WBC count, ESR and CRP had dropped. CT scan after methylprednisolone injection revealed an unexpected increase in the size of the tumor mass. Not only did anterior cortex was much more eroded but the posterior cortex too showed frank invasion of the tumor tissue. Though the tumor tissue was beyond posterior bony confines of manubrium, yet it was not invading adjacent mediastinal sensitive structures.
Figure 2: Presenting X-Rays:

Figure 3: CT scan at presentation:

Figure 4: CT scan at presentation:
Discussion:
The initial probable diagnosis emerged after the first biopsy study was Cysticercosis. *Cysticercosis* disease is caused by the larval form of the *Taenia solium* parasite, known to induce inflammatory sequence, not only in tissues surrounding the parasite, but also quite distant(4) Cysticercosis casts its oncogenic immunosuppressive effect through various pathways viz. differential expression of antigens, molecular mimicry of human leukocyte antigens, and alterations to the human immune system (5) Cysticercosis causes synthesis of proteins that decrease the production of cytokines IL-2, IL-4, and...
IFN-γ and recruitment of macrophages by TNF-α, thereby rendering Th1 and Th2 immune responses and pro-inflammatory cytokines ineffective, which act as the defense mechanism against neoplasia(6). Majority of the tumors thus induced are malignant.

The treating surgeon in this case, not accepting the diagnosis of cysticercosis, sent the biopsy slide for review, that showed the features of Eosinophilic granuloma this time. He found diffuse infiltrated areas of foamy histiocytic cell showing nucleus like groove, surrounded by heavy infiltrate of lymphocytes, some plasma cells and eosinophils. No necrosis or atypical mitosis was observed. Although to confirm eosinophilic granuloma immune-histochemistry was advised but could not be done then.

**Eosinophilic granuloma** is the benign solitary form of overlapping three varieties of Langerhans cell histiocytosis. The other two are Letterer-Siwe disease (multifocal, multisystem) and Hand-Schüller-Christian disease (multifocal, unisystem). Although solitary lesion is more common, multiple lesions in skeleton are seen in skull, mandible, ribs, spine and long bones (7). It may occur from childhood to adult age and usually presents with pain, fever, swelling and leucocytosis. Due to accumulations of histiocytes in the medullary cavity, erosive expansions happen, predisposing to pathological fractures. Since, clinical and radiological evidences are usually inadequate, cytology is essential to arrive at the diagnosis of eosinophilic granuloma. Identification of characteristic Langerhans cells with typical multinucleated forms, alike osteoclasts or touton like giant cells, Langerhans cells with typical multinucleated forms, neutrophils and small lymphocytes (8,9), are most often substantial evidences, with immuno-histochemistry (IHC) study being the decisive component of evaluation. IHC marker in Eosinophilic granuloma S100 and CD1a, both are positive. Though eosinophilic granuloma is radiosensitive, the usual course may extend up to 2 years, for spontaneous resolution.

At this juncture we received the patient with an osteolytic lesion in manubrium, with suspected Eosinophilic granuloma on cytology, but CB NAAT for tuberculosis and IHC confirmation for eosinophilic granuloma pending.

We did a core-needle biopsy of the lesion under image-intensifier. A negative gram stain, negative bacterial culture, negative ZN stain for AFB, and a negative CB NAAT ruled out infections and tuberculosis, finally. On cytology, it revealed more of inflammatory pathology with mainly lymphoplasm and foamy macrophages (appearance after phagocytosis of lipid debris). The immuno-histochemistry turned out as VIMENTIN and $S100$ positive while $CD1a$ was negative. Hence, Xanthomatous Inflammation was concluded, and since it existed in a bone, it was labelled as Xanthomatous Osteomyelitis (XO).

Xanthomatous Osteomyelitis (XO) is a chronic disease, with variable presenting age of onset. Since it manifests as an osteolytic lesion, it usually taken as tuberculosis in developing countries, or as a tumor. Of all the cases reported till now (17 including the present case) in only 5 culture came positive for any growth, 2 staphylococci, 1 case with Pseudomonas 1 with nontyphus Salmonella and 1 with mycobacterium marinum. All the cases reported till date are solitary except BORJIAN et al who reported a bifocal case in fibula and ulna (10) Borjian et al. and Kamat et al. isolated *Staphylococcus aureus*, while Cennimo reported *Mycobacterium marinum* from the lesion. However, no organism was isolated in our case (11).

Since 1984 with the first case by COZZUTTO, only 17 cases have been reported in the worldwide literature including us.

Despite present day advanced imaging modalities, good histo-pathology services with immune-histochemistry backup remain the mainstay to confirm diagnosis. Macrophages and lymphocytes show a marked expression of HLA–DR antigen. Human Leucocyte Antigen-DR was primarily labelled as cell surface antigens that mediates graft-versus-host disease. DR is found in antigen presenting cells (macrophages, B cells and dendritic cells).Since it serves to present foreign peptides to immune system that promotes antibodies production against the same peptides, HLA-DR is also deemed as a marker for immune stimulation(16)

Xanthomatous Inflammation needs to be differentiated from Tubercular osteomyelitis (Gene Expert / CBNAAT is required to rule out ), Eosinophilic Granuloma ($S100$ and $CD1a$ both are positive), Hand Schuller Christian syndrome (diabetes insipidus and exophthalmos found additionally), Pseudo-Xanthomatous inflammation or malakoplakia (characterized by Michaelis-Gutman bodies that stain positive with Von Kossa calcium and Prussian blue stains), Erdheim-Chester disease (histology shows foamy histiocytes, fibrosis without neutrophilic infiltrations, and cholesterol clefts).
We had considered thorough curettage and bone grafting, but since the posterior manubrial wall had already breached, we hesitated and attempted local infiltration of steroid to curb the inflammatory symptoms, to buy time for future excision of

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Age/sex</th>
<th>Site</th>
<th>Radiological finding</th>
<th>Clinical and radiological diagnosis</th>
<th>Organism grown and other findings</th>
<th>Treatment given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cozzuto et al [1]</td>
<td>1984</td>
<td>5/M,14/M</td>
<td>1st Rib; Tibia</td>
<td>X Rays- Osteolytic Lesion; X Rays- Mottled Radiolucency</td>
<td>Ewings Sarcoma And Chronic Osteomyelitis;Chronic Infection</td>
<td>-</td>
<td>En Bloc Resection Of The First Rib; Excision Of The Lesion</td>
</tr>
<tr>
<td>Vankalakunt i et al [12]</td>
<td>2007</td>
<td>50/F</td>
<td>Unlar Diaphysis</td>
<td>X- Rays- Poorly Defined Osteolytic Lesion</td>
<td>Tumor</td>
<td>Histioocytes Positive Kp1,Ham56,Cd11 b,Cd68</td>
<td>Curetage With Bone Grafting</td>
</tr>
<tr>
<td>BORJIAN et al [10]</td>
<td>2012</td>
<td>14/M</td>
<td>HUMERAL HEAD; DIAPHYSIS</td>
<td>Xrays-reaction in the periosteum and disruption of cortex ct-reaction in the periostium and infiltration of bone marrow mri signal abnormalities</td>
<td>MALIGNANCY, OSTEOMYELITIS</td>
<td>STAPHYLOCOCCUS AUREUS</td>
<td>PATIENT LEFT HOSPITAL AGAINST MEDICAL ADVICE</td>
</tr>
<tr>
<td>Nunes et al</td>
<td>2012</td>
<td>56/M</td>
<td>Distal Humeral Metaphysis</td>
<td>Osteolytic Lesion</td>
<td>Tumor</td>
<td>Histioocytes Positive For Cd68</td>
<td>Curetage With Bone Grafting</td>
</tr>
<tr>
<td>Holmes et al [16]</td>
<td>2013</td>
<td>44/M</td>
<td>Distal Tibia</td>
<td>Mass In Soft Tissue</td>
<td>-</td>
<td>-</td>
<td>Curetage</td>
</tr>
<tr>
<td>Nalini et al</td>
<td>2014</td>
<td>20/F</td>
<td>Femur(Peritroch entric Region)</td>
<td>Osteolytic Lesion Itwh Well Defined Margins</td>
<td>-</td>
<td>-</td>
<td>Curetage With Bone Grafting</td>
</tr>
<tr>
<td>Sapra et al [21]</td>
<td>2015</td>
<td>34/M</td>
<td>Medial Malleolus, Talus,Cuboid</td>
<td>Osteoplytic Lesion With Marginal Sclerosis</td>
<td>-</td>
<td>-</td>
<td>Curetage With Bone Grafting</td>
</tr>
<tr>
<td>Singh et al [22]</td>
<td>2015</td>
<td>65/F</td>
<td>Femur(Peritroch entric Region)</td>
<td>Osteolytic Lesion With Well Defined Margins</td>
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<tr>
<td>Arul et al. [18]</td>
<td>2016</td>
<td>20/M</td>
<td>Femur (Peri-Trochentric Region)</td>
<td>Hyperintense Lesion, With Well Defined Margins</td>
<td>-</td>
<td>-</td>
<td>Curetage</td>
</tr>
<tr>
<td>Baisakh et al [20]</td>
<td>2016</td>
<td>21/F</td>
<td>Distal Epiphsysis Of Femur, Proximal Metaphysis of Tibia</td>
<td>Osteolytic Lesions</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Cheena et al [19]</td>
<td>2017</td>
<td>5/F</td>
<td>Humerus</td>
<td>Multiple Osteolytic Lesions</td>
<td>-</td>
<td>Non-Typhus Salmonella</td>
<td>Iv And Oral Antibiotics</td>
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<td>Manchanda et al [Present Case]</td>
<td>2020</td>
<td>24/5</td>
<td>MANUBRIUM STERNI</td>
<td>OSTEOLYTIC LESION With Cortical Breach</td>
<td>EOSINOPHILIC GRANULOMA</td>
<td>NONE</td>
<td>Local STEROID Injection</td>
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manubrium if symptoms arose or lesion found to be rapidly expanding.

Conclusion:

Xanthomatosus osteomyelitis is a very rare disease with only very few cases reported in English literature, moreover it has not been reported as yet in sternum, to the best of our knowledge. It’s osteolytic radiological appearance usually is mistaken for a tumor or infection, hence we strongly advocate immune-histochemistry coupled with cytology, to arrive at the final diagnosis, after all imagings, that are necessary.

References:
