Case Report

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 into 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 Xantho-granulomatous 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 empirically 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 1: Clinical picture at presentation

Figure 2: Presenting X-Rays:

Figure 3: CT scan at presentation:

Figure 4: CT scan at presentation:

Figure 5: CT scan after local injection:

Figure 5: CT scan after local injection:

Figure 6: Clinical picture (9 months after injection)

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 it's 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, 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 upto 2 years, for spontaneous resolution.

At this juncture we received the patient with a 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 non-typhus *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 immuno-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).

Table 1: Characteristics of the different studies reporting the case

Study	Year	Age/sex	Site	Radiological finding	Clinical and radiological diagnosis	Organism grown and other findings	Treatment given
Cozzutto et al [1]	1984	5/M,14/M	1st Rib; Tibia	X Rays- Osteolytic Lesion; X Rays- Mottled Radiolucency	Ewings Sarcoma And Chronic Osteomyelitis; Chronic Infection	-	En Bloc Resection Of The First Rib; Excision Of The Lesion
Vankalakunti et al [12]	2007	50/F	Ulnar Diaphysis	X- Rays- Poorly Defined Osteolytic Lesion	Tumor	Histiocytes Positive Kp1,Ham56,Cd11b,Cd68	Curettage With Bone Grafting
Cennimo et al [15]	2007	41/M	Index Finger And Wrist	X Rays- Swelling Of Soft Tissue Mri- Abscess Formation And Synovial Enhancement	Abscess Formation With The Enhancement Of Synovium	Mycobacterium Marinum Growth From Culture	Antibiotics And Synovectomy
Kamat et al [11]	2011	13/M	Distal Tibia	X Rays-Lytic Lesion In The Submetaphyseal Region With Sclerotic Margin	Brodie's Abscess	Staphylococcus Aureus	Curettage
BORJIAN et al [10]	2012	14/M	HUMERAL HEAD; DIAPHYSIS	Xrays-reaction in the periosteum and disruption of cortex ct-reaction in the periosteum and infiltration of bone marrow mri signal abnormalities	MALIGNANCY, OSTEOMYELITIS	STAPHYLOCOCCUS AUREUS	PATIENT LEFT HOSPITAL AGAINST MEDICAL ADVICE
Nunes et al	2012	56/M	Distal Humeral Metaphysis	Osteolytic Lesion	Tumor	Histiocytes Positive For Cd68	Curettage With Bone Grafting
Holmes et al [16]	2013	44/M	Distal Tibia	Mass In Soft Tissue	-	-	Curettage
Nalini et al	2014	20/F	Femur(Peritrochanteric Region)	Osteolytic Lesion With Well Defined Margins	-	-	Curettage With Bone Grafting
Rathi et al [20]	2014	50/M	Distal Tibia	Osteolytic Lesion With Periosteal Reaction	-	Pseudomonas Grown From Pus Culture	Iv Antibiotics, Arthrodesis
Sapra et al [21]	2015	34/M	Medial Malleolus, Talus,Cuboid	Osteolytic Lesion With Marginal Sclerosis	-	-	Curettage With Bone Grafting
Singh et al [22]	2015	65/F	Femur(Peritrochanteric Region)	Osteolytic Lesion With Well Defined Margins	-	-	
Arul et al. [18]	2016	20/M	Femur (Peritrochanteric Region)	Hyperintense Lesion, With Well Defined Margins	-	-	Curettage
Baisakh et al [20]	2016	21/F	Distal Epiphysis Of Femur, Proximal Metaphysis of Tibia	Osteolytic Lesions	-	-	
Kaeneuchi et al 2017 [17]	36/F	2017	Distal Metaphysis Of Tibia	Osteolytic Lesion With Sclerotic Margins	-		Excisional Biopsy With Curettage
Cheema et al [19]	2017	5/F	Humerus	Multiple Osteolytic Lesions	-	Non-Typhus Salmonella	Iv And Oral Antibiotics
Manchanda et al [Present Case]	2020	24/5	MANUBRIUM STERNI	OSTEOLYTIC LESION With Cortical Breach	EOSINOPHILIC GRANULOMA	NONE	Local STEROID Injection

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

manubrium if symptoms arose or lesion found to be rapidly expanding.

Conclusion:

Xanthomatous 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.

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