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Chronic recurrent multifocal osteomyelitis (CRMO) presenting as non-healing wound: Case report and brief Review of literature

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Abstract

A six year old girl child presented with delayed wound healing in her left elbow weeks after incision & drainage performed elsewhere for suspected sepsis. Radiograph revealed osteitis and osteolysis in the lower end of humerus without sequestrum. Magnetic resonance imaging ruled out possibility of any neoplastic lesion. Wound cultures were repeatedly negative for bacteria, mycobateria and fungi. There was past history of similar painful skin lesions followed by wound healing problems around the knee and the thigh. Months later she presented again with similar non-healing wound after another incision and drainage by another surgeon. Wound margin biopsy showed subacute nonspecific inflammation with prominent neutrophilic infiltration. After interdisciplinary review diagnosis of chronic recurrent multifocal osteomyelitis **(**CRMO) was entertained by a diagnosis of exclusion. Due to its rarity, one may be unfamiliar with this elusive entity and a high index of suspicion is required to reduce diagnostic dilemma. Although generally a self-limiting disease, CRMO can have a prolonged course and result in significant morbidity. Immune targeted therapy helped the child heal her wound. CRMO should be considered in the differential diagnosis, once neoplasm and sepsis are excluded in recurrent inflammatory skin lesions with osteitis. This can help minimize the number of unnecessary interventions in the form of repeated biopsies, repeated debridement, surgeries and antibiotic therapy. Whenever possible, incision and drainage should be avoided in this auto inflammatory condition to avoid unpredictable course of wound healing.

Keywords: Chronic recurrent multifocal osteomyelitis, Wound healing, Aseptic osteomyelitis, Chronic mutifocal periosteitis and arthropathy.

Introduction

Originally propounded as autoimmune condition, CRMO is rather a rare group of auto-inflammatory disorder of children and young adults that is characterized by aseptic osteomyelitis. The disease typically presents with multifocal bone pain secondary to sterile osseous inflammation with a relapsing and remitting course. It is a rare systemic, non-purulent inflammatory disease that predominantly involves the metaphysis of long bones, pelvis or spine.[(1)] It is characterized by chronic multifocal nonbacterial osteomyelitis of obscure origin and there may be concomitant or intermittent skin pustulosis which resolves in most cases.[(2)] Due to dual system involvements, it is also sometimes called as *Skibo* disease (skin-bone disease).[(2)] Due to overlapping clinical radiological and pathological features, several unclassified disease entities are now being increasingly included in a common group or entity called chronic mutifocal periosteitis and arthropathy. This group includes CRMO, SAPHO Syndrome (Synovitis, acne, pustulosis, hyperostosis and osteitis), and SCCH (sternocostoclavicular hyperostosis).[(3)] Another syndrome akin to this group is Majeed syndrome to which our patient was quite similar except the absence of congenital dyserythropoetic aneamia and classical sweet syndrome.[(4)] CRMO patients typically present with multifocal bone pain secondary to sterile osseous inflammation, and the disease has a relapsing and remitting course.[(5)] The cause of CRMO remains unclear, although the results of several studies have suggested a genetic component.[(4,5)]

Case Report

A 6 year old first born girl had delayed wound healing after an incision and drainage performed elsewhere six weeks back for suspected sepsis around the lateral aspect of her left elbow (Fig. 1). There was accompanying pain around the elbow, low grade fever but no malaise.

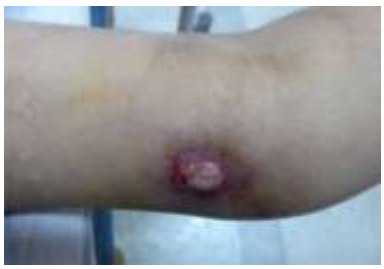

Fig. 1: Non-healing wound following incision and drainage: lateral aspect of the left elbow

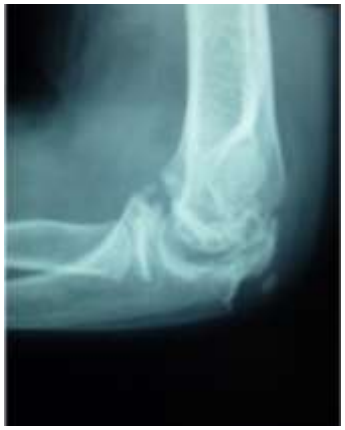

Fig. 2: Radiograph showing osteitis, lower end of the humerus but no sequestrum

Radiograph showed evidence of osteitis, mild osteolysis in the lower end of left humerus without any sequestrum (Fig. 2). Routine blood tests revealed anaemia; Haemoglobin of 7.2 gm% and high Erythrocytic sedimentation rate (112mm/ hour). Total Leucocyte count was 6000 only. Differential leucocyte count showed lymphocytic leucocytosis (41%). C-reactive protein was positive (41.8 mg %). Coagulation profile was normal. Wound swab cultures were repetitively negative for any bacteria but microscopy showed 2-5 pus cells /HPF. On examination the wound had exuberant granulation tissues with white tenacious materials in its centre. There was serous discharge, but no frank pus formation. Exuberant granulation tissues reformed every third day or so after every debridement. Despite repeated debridement and dressing the wound did not heal, although it looked better. Regional lymph-nodes were not enlarged. The liver and spleen were not clinically palpable.

Differential diagnoses kept in mind were atypical infections, disseminated tuberculosis, haemophilia, bony neoplasms and scurvy. In the mean time, culture for both mycobacteria and fungi came negative from the laboratory. Peripheral blood smears showed normocytic to microcytic hypochromic anemia only. MRI of the left elbow showed aseptic osteomyelitis without intraosseous abscess or necrotic sequestrum and ruled out neoplastic lesions. There was MR finding of marrow edema in proximal ulna and radius with joint effusion in elbow. There was linear symmetrical subperiosteal hyperintensity along the humeral metadiaphysis as well. Heamoglobin typing using electrophoresis was normal thus excluding haemoglobinopathies. The IgE level was in normal range is less than 81 kU/l. HIV tests were negative.

About a week later she also complained of pain in her left ankle. On examination there was swelling and erythema around the antero-lateral aspect of the joint. The intravenous cannula site of her right wrist also developed erythema, pain, and signs of possible sepsis. Culture of the cannula tip and swab from the cannulation site however did not reveal any pyogenic bacteria. Skin margin biopsy from the wound showed features of acute suppurative nonspecific inflammation with neutrophilic aggregates.

In the mean time her old medical records at age 2 from her earlier hospital was obtained. The proximal tibia was involved at that age and Tc 99 m bone scan showed increased flow and blood pool concentration over the left elbow with abnormal concentration over the epiphysis and metaphysic of proximal tibia. Old biopsy record from the left tibial lesion showed chronic inflammatory granulation tissue along with focal fibrosis and clusters of foamy and epitheloids - histiocytes mixed with lymphocytes. In the earlier core biopsy sample from the bony lesion Gomori's methenamine silverstain was negative for fungi. Nitroblue tetrazolium reduction test for chronic granulomatous diseases was done by earlier surgeon but the result was normal (6%).

The mother provided past history of recurrent erythema followed by pustular lesion and wound healing problem at the site of DPT (diphtheria, pertussis,tetanus) vaccination sites with delayed wound healing and odd looking scars during early infancy. At about the age of 4 & half years similar delayed wound healing occurred after surgical drainage near right upper leg. Just after the age of 5 years she had yet another skin lesion near the iliac crest that was managed conservatively. There was no past history of pneumonia or major organ or systemic infection. There was no history of jaundice in infancy or early childhood. There was no history of blood transfusions during infancy or early childhood. All previous skin lesions healed with a glistening cigarette paper like residual scar.

Taking into consideration the recurrent episodes, repeated sterile swab cultures, radiological bony sclerotic changes in absence of sequestrum and in absence of systemic signs of sepsis a working diagnosis of CRMO was made and treatment initiated accordingly. On the basis of available current literature review NSAID (Ibuprofen), Azithromycin syrup 200 mg once daily were started. After a couple of debridements followed by regular dressings and medications the wound slowly started to heal. She was discharged home. She was given salfasalazine, low dose oral steroid 5 mg once daily, pulse pamidronate therapy, followed by NSAIDs (Piroxicam). The intravenous pamidronate infusion therapy consisted of a 3-day treatment regime (infusion of 30 mg over two hours initially) planned for every 3 months, with a maximum cumulative dose of no more than 11.5 mg/kg/year. The pain around the elbow diminished but the wound was not healing. Pain in her left ankle with accompanying mild swelling continued. The final healing of the wound occurred after three and a half months with repeated cauterization with copper sulfate to control the exuberant granulations. Healing occurred

with prominent residual hypopigmented cigarette paper like scars. There was loss of elbow range of motion by 30^0 degree with a residual ROM between 20^0- 135^0.

A year later after attaining 7 years of age she visited our hospital again with another non-healing wound around the same (left) elbow despite her being on multiple anti-inflammatory drugs described above. White discharge continued from the wound despite repeated dressings. There was no accompanying fever. Multiple serial wound swab cultures were negative. Radiograph showed evidence of osteitis, mild osteolysis in the lower end of left humerus with sclerosis of radial head epiphysis, but no sequestrum. Wound swab cultures for mycobacterium or fungus were negative again. Biopsy taken from the lesion with a 'healthy' margin showed nonspecific inflammation with predominant neutrophilic infiltartion. Further treatment involved regular antiseptic dressing, oral Naproxan, low dose corticosteroids and salfasalazine. The wound healing progressed well with three repeated dressings, secondary closure with loosely placed sutures allowing room for drainage over period of next three weeks leaving behind a cigarette paper like scar (Fig. 3). Finally the diagnosis was reviewed as CRMO by a diagnosis of exclusion. Counseling of the family regarding the natural history, aseptic nature of the disease, treatment options and prognostication were done on the basis of currently available information from medical literature.

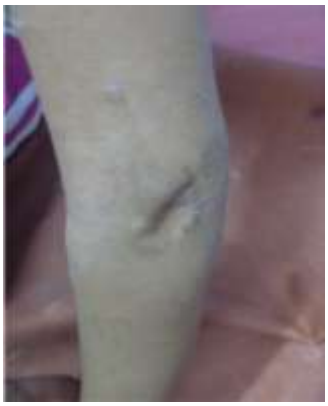

Fig. 3: Final healing by secondary intention after months with prominent residual hypopigmented cigarette paper like scar

The patient was started on Naproxen, low dose corticosteroid and pulse pamidronate therapy with good response. Long term proton pump inhibitor was added to reduce potential risk of gastro-intestinal complication of combining NSAIDs and steroid. There was no evidence of bowel involvement like Crohn's diseases or Ulcerative colitis like lesions reported with some CRMO cases. There was no acne or pustular lesion in palms or soles.

Discussion

Diagnosing and treating patient with CRMO and related entities as the primary physician may be challenging. The cause of CRMO remains unclear, although several studies have suggested a genetic component. CRMO is a chronic multifocal non-bacterial osteomyelitis of obscure origin and it may be accompanied by concomitant or intermittent skin pustulosis which mostly tend to resolve.[2] The term CRMO was first used by Probst and colleagues and encompasses the typical clinical features of this entity: chronicity with a protracted course, involvement of more than one site, multiple exacerbations and relapses at old and new sites, and disease at sites that are typical of osteomyelitis in children.[5] Familiarity of the disease with the clinicians may lead to early diagnosis. This systemic inflammatory disease mainly occurs in the metaphyses of long bones, in pelvic bones or spine (as spondylitis) and is characterized by nonbacterial, non-purulent osteomyelitis.[1] The disease process is a primarily chronic sterile inflammation and the onset is often monostotic (e.g. clavicle) and later evolves frequently to polyostotic form of aseptic osteomyelitis. Possible trigger is by an immuno-pathological process induced by *Proprionibacterium acnes*, that shows plasma cellular invasion histologically and a sclerosing process in different stages.[1] Although generally a self-limiting disease, CRMO can have a prolonged course and result in significant morbidity.[5]

Association with pustulous dermatosis (psoriasis, acne, palmo-plantar pustulosis) is found in about 25% of children and adolescents of CRMO and in more than 50% of the adult patients.[1] A growing body of literature has identified the association between neutrophilic dermatoses (sweet syndrome) and multifocal aseptic bone lesions in children with CRMO.[6] The term 'neutrophilic dermatosis' (ND) was initially used by R. D. Sweet in 1964 as 'acute febrile neutrophilic dermatosis' to describe *Sweet's syndrome*. However, over the years, this terminology has been adapted to denote non-infective dermatoses that exhibit a predominantly neutrophilic inflammatory infiltrate and promptly respond to corticosteroid therapy. Largely, dermatoses with associated vasculitis are not included in this spectrum. The prevalence of skin lesions like palmoplantar pustulosis is much higher in SAPHO syndrome than in CRMO. Furthermore, the skin lesions may manifest several years after the first bone lesion in children with CRMO. Classically, patients present with swelling, pain, and impaired mobility of the affected area, with skin lesions developing concurrently or later. Our patient had a concomitant skin lesion around the involved elbow.[6] Our patient had no palmoplantar pustulosis. Neutrophilic skin infiltration was documented in biopsy. But absence of any fever excluded classical sweet syndrome. Pathergy is the term used to describe hyper-reactivity of the skin that occurs in response to

minimal trauma.[9] Pathergy is not a classical association with CRMO; but in our case this co-morbidity was suggested by development of aseptic pustular lesion preceded by erythema following minor trauma of vaccination and intravenous cannulations etc. A positive skin pathergy test (SPT), characterised by erythematous induration at the site of the needle stick with a small pustule containing sterile pus at its centre, is among the criteria required for a diagnosis. Pathergy lesions, the development of new skin lesions or the aggravation of existing ones following trivial trauma, are also reported in neutrophilic dermatoses such as Sweet's syndrome and Behcet's syndrome and also in pyoderma gangrenosum.[9]

SAPHO syndrome seen commonly in adult, lie along the same clinical spectrum.[3,6] In fact some believe that CRMO is the pediatric presentation of SAPHO.[5,6] CRMO typically manifests in the first decade of life, the mean age of onset for SAPHO syndrome is 28 years. However, adults with CRMO and children with SAPHO syndrome have been reported.[5] The two syndromes share lot of common characteristics, including osteitis, a unifocal or multifocal presentation, hyperostosis, and pustulosis.[6] The term chronic non-bacterial osteomyelitis (CNO) is reserved for a clinical entity of CRMO affecting mainly adolescents; that may have a unifocal or multifocal occurrence.[7] Owing to the lack of a diagnostic test however, the diagnosis of CRMO remains basically a diagnosis of exclusion.[5] It is therefore important to exclude lesion of infectious origin and musculoskeletal neoplasms that may mimic CRMO initially. Because its etiology is largely unknown, the diagnosis is still based on clinical criteria; treatment is empiric and not always successful.[8] The histologic findings in bone biopsies are nonspecific, showing inflammatory changes with granulocytic infiltration.[8]

Radiologists can be the first to suggest this diagnosis given its characteristic radiographic appearance[5] and distribution of disease. But not all radiologists will be familiar with the typical imaging findings of CRMO especially if clinical data is not provided well; an experienced radiologist familiar with this entity actually may be instrumental to prevent unnecessary multiple biopsies and long-term antibiotic treatment in children with CRMO.[5] CRMO is often bilateral and multifocal at presentation. The diagnosis is supported by the presence of osteolytic lesions with surrounding sclerosis apparent on radiographs, and silent asymptomatic lesions frequently appear on nuclear scans. The typical imaging findings of CRMO include lytic and sclerotic lesions in the metaphyses of long bones and the medial clavicles. The typical radiographic appearance is a lytic lesion at a metaphysis or metaphyseal equivalent that develops progressive sclerosis and hyperostosis over time. Other common sites of disease are the vertebral bodies, pelvis, ribs, and mandible.[5] MRI may easily exclude neoplasms from the differential diagnosis. Five different types of distribution of osteomyelitic lesions may be found by using Tc 99m-bone scan; "pelvic type" is the most common.[1] Because of the close neighbourhood of meta-/epiphyseal osteomyelitic focuses, "sympathetic arthritis" with synovitis is seen frequently.[1] The presence of disease in typical sites such as the medial clavicle, the presence of bilateral disease in a symmetric distribution, and the presence of skin findings such as palmo-plantar pustulosis (more common in adult form/SAPHO) support the diagnosis of CRMO.[5] For obvious reasons patients of CRMO are refractory to antibiotic therapy, but reported they dramatically respond to systemic steroids and often need maintenance therapy on low-dose steroid to prevent relapse.[6] Clavicular involvements can be an important clue.[3] But in our case the clavicles were not involved clinically.

Recent literature recommends that *Chronic mutifocal periosteitis and arthropathy* may be a better terminology to encompass all these entities and this may lead to better awareness, early diagnosis, option for better research and hopefully better treatment of CRMO.[3] Along with the variability in its initial presentation, there is great variability in the numbers of sites affected, recurrence rates, and prognosis.[5] The typical clinical picture of CRMO is a child or young adult with a history of chronic multifocal bone pain, in whom biopsy of osseous lesions shows osteomyelitis with failure to culture any organisms. The very rare variety called Majeed syndrome is characterized by chronic recurrent multifocal osteomyelitis that is of early onset with a lifelong course, congenital dyserythropoietic anemia (CDA) that presents as hypochromic, microcytic anemia (ranges from mild to transfusion-dependent) during the first year of life and transient inflammatory dermatosis, often manifesting as Sweet syndrome (neutrophilic skin infiltration).[4] With the exception of CRMO in the context of *Majeed syndrome* that is associated with a *congenital dyserythropoetic anemia*, there is no diagnostic test for CRMO and it still remains a diagnosis of exclusion. Several observations suggest the contribution of genetic factors to the etiology of chronic recurrent multifocal osteomyelitis. Indeed, mutations in LPIN2 cause the syndromic form of chronic recurrent multifocal osteomyelitis: the Majeed syndrome.

Differential diagnosis may include several entities including bone malignancies like osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma and histiocytosis.[7] Radiologists need to be familiar with the imaging findings because they may be the first to suggest this diagnosis. This can help minimize the number of unnecessary interventions in the form of repeated biopsies, surgeries, and antibiotic therapy.[5] Early diagnosis of CRMO therefore requires a team approach between the clinicians and diagnostic departments besides a high index of suspicion.

CRMO is treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy to avoid disuse atrophy of muscles and contractures.[4] If CRMO does not respond to NSAIDs, short term corticosteroids can be used to control bone and skin manifestations. However, the complications of long-term use of corticosteroids limit their use in children.[2,4] Accompanying congenital dyserythropoietic anemia that presents as hypochromic, microcytic anemia during the first year of life ranging from mild to transfusion-dependent anemia is treated with red blood cell transfusion if indicated in cases of CRMO of Majeed syndrome.[4] Since chronic recurrent multifocal osteomyelitis is an auto-inflammatory disorder characterized by bone pain and fever, a course of exacerbations and remissions and a frequent association with other inflammatory conditions,[8] therapeutic approach with NSAIDS, azithromycine, biphosphonates, steroids and calcitonine are reported in the literature with varying degree of success.[1]

There are recent reports of Pamidronate being administered as intravenous cycles to treat painful CRMO. The dose of pamidronate varied among subjects but was given as monthly to every 3 monthly cycles depending on the distance the patient lived from the treating center. The ideal dose schedule for CRMO is not established but the maximum cumulative dose is $\leq$ 11.5 mg/kg/year.[10] Pamidronate treatment has been proposed as effective second line therapy and such therapy may be continued until resolution of MRI documented bone inflammation.[10] Bisphosphonates possibly neutralizes the nociceptive acidic environment rapidly by inactivating osteoclasts, a mechanism that may explain the rapid pain relief in some patients. The prompt improvement in soft tissue swelling adjacent to bone lesions was observed in CRMO patients, most likely reflecting the anti-cytokine effects of pamidronate.[10]

Conclusion

CRMO is an established clinicopathologic entity, although its cause remains elusive. Diagnosis of CRMO is basically by a process of exclusion. Diagnosis of CRMO may be difficult in early or first presentations. Orthopaedicians, paediatricians, dermatologist may be unfamiliar with this rather obscure disease entity and therefore high index of suspicion is required for making a timely diagnosis. Once bacterial sepsis and neoplasm are excluded by appropriate tests in any recurrent atypical skin lesions or non-healing wounds with underlying osteitis in paediatic age group CRMO should be considered as a differential diagnosis. Our case is not only rare but atypical too because of 1) early evidence of pathergy after vaccination in early childhood and 2) tendency for peripheral bone involvement. Notably, the clavicles, spine and the sternum were not involved 3) Cigarette paper like scar after healing was noted in all healed lesions.

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