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S-100 POSITIVE MULTICENTRIC RETICULOHISTIOCYTOSIS – REPORT OF A RARE CASE WITH BRIEF REVIEW OF LITERATURE

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Abstract
Background: Multicentric reticulohistiocytosis (MRH) is a rare histiocytic proliferative disorder involving skin, mucosa and joints. Diagnosis is confirmed by histopathological examination.
Case Report: A 45 year old patient presented with non-pruritic papules over the body and multiple joint pains. Histopathologically, the lesion was composed of oncocytic macrophages and multinucleate giant cells with abundant, eosinophilic and granular cytoplasm with ground glass appearance. Immunohistochemical expression for CD-68 and S-100 was seen .
Conclusion: We describe a case of MRH along with brief review of literature with unusual immunohistochemical expression of S-100 protein which is reported negative in majority of previously presented cases, however CD68 positivity confirmed the non-langerhans cell origin.

Key words: Multicentric reticulohistiocytosis; Skin nodules; Arthritis; S-100

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Introduction

Multicentric reticulohistiocytosis (MRH) is a rare histiocytic proliferative disorder of unknown etiology usually manifesting as skin nodules and progressive arthritis. Although first described by Caro and Senear [1] in 1952 as "reticulohistiocytic granuloma", the term MRH was first given by Goltz and Laymon [2] in 1954 because of its multifocal origin and systemic involvement. Characterstically, MRH presents with papulo-nodular skin eruptions with a predilection for hands and destructive, deforming, symmetrical polyarthritis [3]. The diagnosis is confirmed histologically by the presence of infiltrative histiocytic multinucleated giant cell with eosinophilic, ground glass cytoplasm [4] which stain positive for Periodic-acid Schiff. Immunohistochemistry (IHC) reveals positivity for markers of monocyte or macrophage origin [5]. There is no consistently effective treatment established [6], however systemic steroids and cytotoxic drugs are tried with variable success. We report this case for its rarity, striking skin lesions and minimal joint involvement and the unusual expression of S-100.

Case Report

A 45 year old man came to the OPD with the complaints of asymptomatic skin-colored, non-pruritic papules over face and body for two and half months. Lesion started over the forehead, progressively increased in number and size to involve the scalp, face, trunk and lower limb. Patient also complained of multiple joint pains involving the knee, shoulder, elbow and hip joint. He was treated with oral steroids and parenteral antibiotics by a local doctor but did not show improvement. Cutaneous examination showed multiple skin colored to reddish, firm papules sized 2-5 mm over the scalp, face, trunk, dorsal aspect of palms and legs (Fig. 1).

Oral cavity showed linear hyperpigmented macules over upper and lower lip. Palms, soles and genitals were spared. There was no joint deformity. Routine biochemical and hematological investigations were normal. ESR was 44mm of Hg at the end of one hr. Histopathology of skin biopsy showed thinned out epidermis overlying a lesion in dermis composed of oncocytic macrophages, few multinucleate giant cells with abundant, eosinophilic, finely granular cytoplasm with ground glass appearance along with diffuse mixed inflammatory infiltrate (Fig. 2).

The oncocytic macrophages were positive for periodic acid-Schiff stain. IHC showed positivity for CD68 and S-100 (Figs 3, 4).

On further evaluation lipid profile, C-reactive protein, rheumatoid factor, ANA profile, chest X-ray, ultrasound abdomen, gastroscopy and bone marrow examination were normal. A diagnosis of MRH was given. Patient was put on Methotrexate, Hydrochloroquin and Folic acid. He responded well to the treatment and the skin lesions regressed. Patient was on regular follow up.

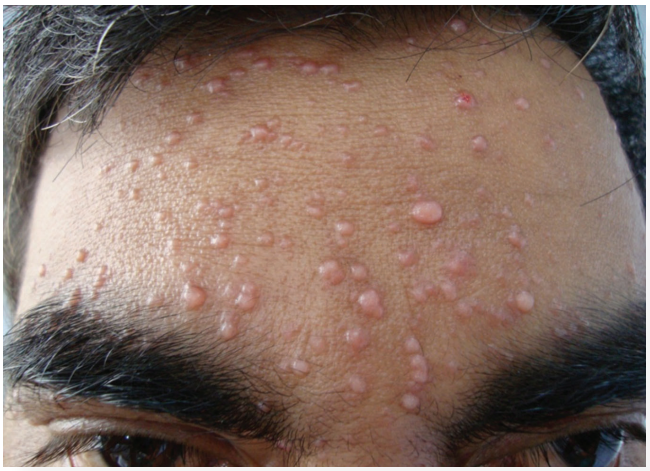

Figure 1. Multiple firm non-pruritic papules over the forehead.

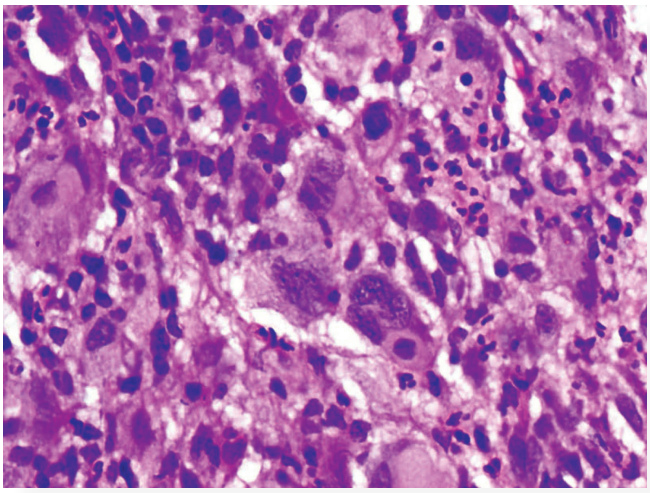

Figure 2. Multinucleate giant cells, oncocytic macrophages, with ground glass appearance. (H&E)

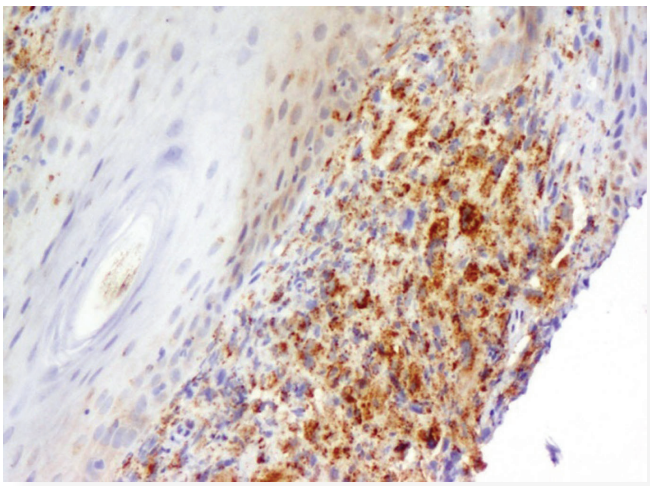

Figure 3. CD-68 positivity establishing non-langerhans cell origin. (x 200)

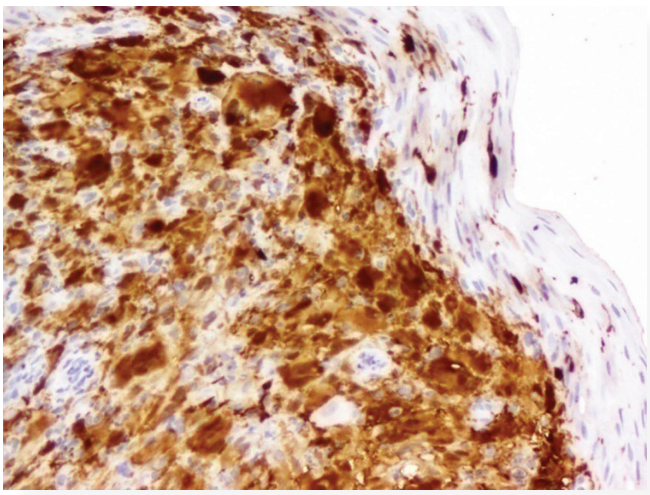

Figure 4. S-100 positivity in oncocytic macrophages. (x 200)

Discussion

Histiocytosis is broadly classified into type I- langerhans cell histiocytosis, type IIa- histiocytes involving cells of dermal dendrocyte lineage, type IIb- histiocytes involving cells other than langerhans cell and dermal dendrocytes, and type III- malignant histiocytic disorders [7].

MRH also known as lipoid dermatoarthritis, lipoid rheumatism and giant cell reticulohistiocytosis is a rare systemic disease of unknown etiology [4,8]. Less than 200 cases have been reported in literature [3]. MRH is proliferative disease, because of its rarity and the absence of any infectious agents, possibility of individual predisposition was considered [9]. MRH has a worldwide distribution with female predominance (60-75 %). It usually begins during the fourth decade of life and presents with polyarthritis (50% of cases), cutaneous lesions (25%) or concurrent arthritis and skin manifestations (25%) [3]. MRH is characterized by proliferation of resident mononuclear phagocytes other than langerhans cells which may be due to the release of monokines, cytokines and other secretory products by unregulated macrophage activation, causing pro-inflammatory actions [8].

Characterstic skin lesions are non-pruritic nodules, commonly seen on the extremities. On the face, these papules may coalesce producing leonine facies. Many small papules along the nail fold create the "coral bead" sign [10]. The polyarthritis may be mild or severe. It may be mutilating, especially on the hands, through destruction of articular cartilage and subarticular bone. The disease tends to wax and wane over years with mutilating arthritis and disfigurement [10].

This case is unique as there was minimal joint involvement. Mucosal surfaces are involved in about 50% cases.

Oropharyngeal, nasal mucosa and tongue are most commonly affected [5]. Our patient showed mucosal involvement. MRH can also involve muscles, tendon sheaths, lymph nodes, bone marrow, eyes, salivary glands, larynx and thyroid6. It is found to be associated with diabetes (6%), hypothyroidism (6%), Sjogren's syndrome, primary biliary cirrhosis, tuberculosis (6%), pregnancy and malignancy in 25% of cases [3,6]. It has been proposed that MRH may be similar to a paraneoplastic syndrome [11] and may be the presenting feature of an undetected malignancy [12]. Our patient showed involvement of skin, mucosa and minimal joint involvement. No underlying disease or malignancy was detected. Radiology of bone lesions in MRH shows bilateral symmetric joint involvement with predeliction for metacarpophalangeal and interphalangeal joints. Bony destruction is disproportionate compared to articular cartilage loss [6]. Osteoporosis and periosteal new bone formation is absent, differentiating it from other inflammatory arthritis [8]. However this case did not show any joint deformity. Diagnosis of MRH is made on histology with the lesion showing presence of numerous multinucleate giant cells and oncocytic macrophages with abundant eosinophilic, finely granular cytoplasm with ground glass appearance. Older lesions show giant cells and fibrosis [10]. The histiocytic multinucleated giant cells contain diastase-resistant, periodic acid Schiff (PAS)–reactive material suggesting a polysaccharide component other than glycogen or acid mucopolysaccharide [13]. IHC of these cells shows a monocyte and macrophage origin and stain positive for CD68, HAM56, Mac387, alpha 1-antitrypsin, CD11b, CD11c, CD14 and CD15. S-100 and CD1a are negative and hence support a non-langerhans cell histiocytic origin [8]. Our case showed positivity for PAS-DR, CD-68 and was interestingly positive for S-100 as well. This is also been described by Miettinen and Fetsch [14] as focal expression in a few cases in a series of 44 biopsies and by few others [15-17]. According to Sidoroff et al. [18] generalized eruptive histiocytoma seems to be an early indeterminate stage of various non-X histiocytic syndromes. Presently it is difficult to assess if S-100 positivity can help in establishing the definitive diagnosis of MRH. However in this patient diagnosis of MRH was based on other pronounced histological and clinical features.

Clinically, differential diagnosis of MRH includes lepromatous leprosy, sarcoidosis, xanthomatosis, histiocytosis X, juvenile and adult xanthogranuloma, generalized eruptive histiocytoma, familial histiocytic dermatoarthritis, and neurofibromatosis. The presence of skin lesions with erosive arthritis differentiates MRH from these diseases. The characterstic histological picture along with IHC helps in confirming the diagnosis. Xanthalesma is associated in one third of patients with MRH and can be confused with familial dyslipidemia, the papulo-nodules can be mistaken for xanthomas, however, lipid profile helps in the differentiation. Lepromatous leprosy presenting with nodular lesions can be differentiated by slit skin smear examination and skin biopsy [8]. Radiologically, MRH can be differentiated from rheumatoid arthritis by the absence of periarticular osteoporosis and early joint space loss. Also rapidly destructive arthritis with joint deformities, characteristic skin lesions and a negative rheumatoid factor helps in differentiation [3]. A case of MRH with positive anticyclic citrullinated antibodies in described by Chauhan A et al. [11]. Our patient was negative for rheumatoid factor and ANA profile was within normal limits.

Although MRH can spontaneously resolve in 5–10 years [11] the natural course of the disease may result in severe destructive arthropathy and disfiguring cutaneous lesions [19]. There is no effective treatment for MRH. Several treatment regimens have been tried but the efficacy is difficult to assess due to disease fluctuations and spontaneous remissions [3]. Systemic steroids, cytotoxic drugs like cyclophosphamide, chlorambucil, methotrexate, etanercept and infliximab, biphosphonates like alendronate and zolidronate are reported to be effective [6]. In our case Methotrexate was given and skin lesions were regressed and the patient responded well.

Conclusion

MRH is a rare histiocytic proliferative disorder of unknown etiology with characteristic clinical features. It may be associated with systemic diseases or underlying malignancy. Diagnosis is confirmed on histopathological examination with characterstic oncocytic macrophages with abundant, eoisinophilic, ground glass cytoplasm staining positive for PAS-DR and CD-68. Some cases are reported to show positivity for S-100 protein. Further studies are required to establish the utility of S-100 positivity in establishing the diagnosis. MRH resolves spontaneously but can result in destructive arthropathy and disfigurement.

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