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Case Report

Multicentric Reticulohistiocytosis in a Patient with Psoriatic Arthritis - Case Report and Literature Review

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Abstract:

Multicentric reticulohistiocytosis (MRH) is a rare systemic disease of unknown etiology, characterized by the proliferation of histiocytes. Typical manifestation includes skin lesions in the form of papules and nodules accompanied by preceding polyarthritis. MRH is also associated with the co-occurrence of malignant tumors and autoimmune diseases, which can significantly complicate the diagnosis. A case of MRH associated with psoriatic arthritis is presented along with review of the literature. Authors attempted to discuss the main challenges presented by the MRH, which are diagnostics, differential diagnosis and treatment. Nevertheless, further studies are necessary to create a better understanding of this challenging disease.

Key words: multicentric reticulohistiocytosis; psoriatic arthritis; non-Langerhans cell histiocytosis; treatment

Introduction

Multicentric reticulohistiocytosis (MRH) is a rare systemic disease of unknown etiology, characterized by the proliferation of histiocytes not deriving from Langerhans cells [1]. The clinical course predominantly involves skin, joints and mucous membranes [2]. Characteristic clinical manifestation includes skin lesions in the form of nodules and papules, usually affecting the dorsal surfaces of the hands, with preceding erosive arthritis leading to severe joint destruction in almost half of the patients [1]. Additionally, studies have shown a strong correlation between the occurrence of MRH and autoimmune diseases – especially Sjögren's syndrome. Moreover, approximately 1/3 of patients develop cancer. The treatment of MRH is a major challenge due to the lack of official treatment guidelines and the unknown etiology of the disease [3]. Early recognition and treatment is crucial to prevent disability, as well as appropriate malignancy screening [1]. We arrived at the correct diagnosis by integrating skin histopathology, immunohistochemistry, and other clinical examinations. The aim of the article is to describe a rare dermatological disease – multicentric reticulohistiocytosis with literature review.

Case Presentation

A 38-year-old patient was admitted to the Dermatology Department due to nodular and papulonodular skin lesions accompanied by severe itching. The lesions were symmetrically on the arms, forearms, hands' dorsum, and nail folds.

At age 18, the patient was diagnosed with psoriasis and psoriatic arthritis (PsA). The patient reported that the joint pain had worsened significantly several months before admission. The pain affected the symmetrical joints: shoulders, elbows, small joints of the hands, knees, and ankles.

During a previous hospitalization in the Rheumatology Clinic, laboratory tests had shown a positive result for antinuclear antibodies (ANA) with a titer of 1:640 and speckled fluorescence pattern and positive results for Sjögren's-syndrome-related antigen A autoantibodies (anti-SS-A). The results of rheumatoid factor (RF), antibodies against cyclic citrullinated peptide (anti-CCP), antibodies against antineutrophil cytoplasmic antibodies (ANCA) were negative. Histopathological examination of the salivary gland did not confirm Sjögren's syndrome. Ultrasonographic examination of the shoulders and hands joints revealed signs of polyarthritis. Physical examination showed bluish, purple nodular, and papulonodular skin lesions measuring about 2 to 8 mm in diameter [Fig. 1]. These lesions were painful upon palpation. A few light-red psoriatic plaques were noted on the lumbar region's skin and the right lower limb. No changes were observed on the mucous membranes or nails.

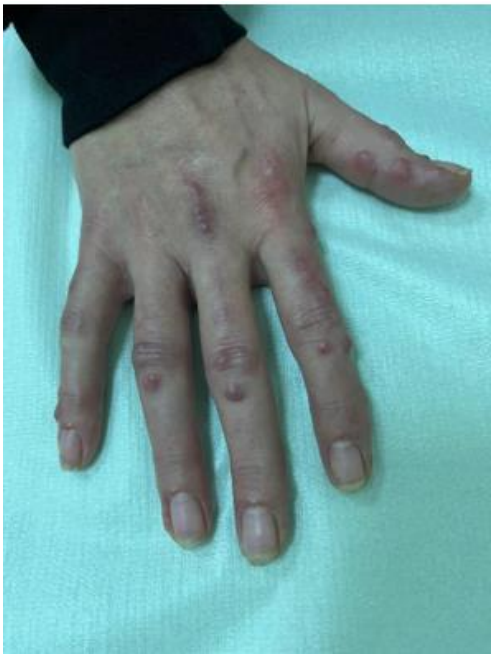

Figure 1: Nodular and papulonodular skin lesions on the dorsum of the right hand.

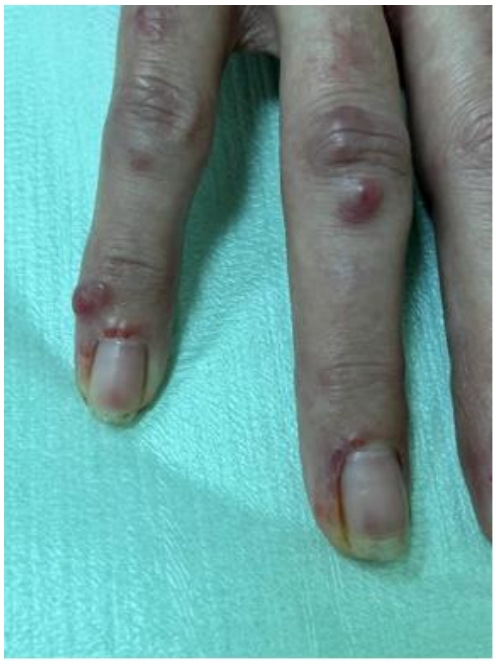

Figure 2: Coalescing papulonodular skin lesions around the nail folds of finger IV and V of the right hand. 'Coral beads' or 'string of pearls' appearance.

Laboratory tests revealed a slightly increased carcinoembryonic antigen (CEA) level (7.3 ng/ml, N: <3 ng/ml). A computed tomography (CT) scan of the chest, abdomen, and pelvis, along with colonoscopy and gastroscopy, revealed no clinically significant anomalies. Histopathological examination of the material collected from the back of the III finger of the right hand, revealed numerous large, malformed, multinucleated histiocytes with eosinophilic cytoplasm, fine granules resembling "ground glass", positive for CD68 antigen and negative for S-100 protein. Based on the results the diagnosis of multicentric reticulohistiocytosis was confirmed. The treatment included methotrexate at a dose of 15 mg/week, prednisolone at a dose of 25 mg/day and celecoxib 400 mg/day. Following treatment, initial improvement in joint pain was achieved. The patient remains under the care of the Dermatology and Rheumatology Clinic.

Discussion

In 2016, the Histiocyte Society proposed a revised classification system for diseases from the histiocytosis group, in which MRH was classified as non-Langerhans cell histiocytosis - group C [4] [Table 1]. MRH is diagnosed extremely rarely. So far, approximately 300 cases of the disease have been described in the literature. MRH occurs three times more often in women than men, with the average age of onset of the first symptoms from circa 40 to 50 years of age [1].

Group	Subtypes	Description
L Group (Langerhans-related)	LCH ECD Mixed LCH and ECD	Disorders characterized by mutations in the MAPK pathway and frequent BRAF V600E mutations.
C Group (Cutaneous and mucocutaneous)	JXG RDD NXG	Primarily involves skin with limited systemic involvement.
R Group (Rosai-Dorfman)	Nodal RDD Extranodal RDD Neoplasia-associated RDD Immune disease-associated RDD	Frequently affects lymph nodes, sometimes with systemic symptoms.
M Group (Malignant Histiocytosis)	Primary Malignant Histiocytoses Secondary Malignant Histiocytosis	Includes rare malignant histiocytic neoplasms.
H Group (Hemophagocytic Lymphohistiocytosis)	Primary HLH Secondary HLH	Involves excessive immune activation and inflammation.

Table 1: Histiocyte Society classification of histiocytic disorders [4].

Note: ECD, Erdheim–Chester disease; HD, histiocytic disorder; HLH, hemophagocytic lymphohistiocytosis; JXG, Juvenile Xanthogranuloma; LCH, Langerhans cell histiocytosis; NXG, Necrobiotic xanthogranuloma; RDD, Rosai–Dorfman disease

Typically, skin lesions are firm, skin-colored, brown-red, purple-red [1] or yellow [2] nodules or papules. The most frequent location of the lesions is the dorsal surface of the hand, affecting 87% of patients [3]. Less frequently, they may appear on the face, trunk, arms and lower limbs [2]. Moreover, there have been reports of small nodular lesions appearing on the mucous membrane of the oral cavity, epiglottis and larynx. The pathognomonic sign of MRH, coalescing periungual papulonodular skin lesions, called ‘coral beads’ or ‘string of pearls” [1]. Skin lesions may be accompanied by pruritus, occurring in 22-46% of cases [1,3]. Typically, skin lesions usually follow articular involvement after an average of 3 years in the majority of patients MRH may typically enter remission, with or without treatment, after an average of 8 years [5]

Joints are affected in 82-92% of patients, while skin involvement is noted in 96% of cases during the clinical progression of MRH. [1,3]. In about 2/3 of cases, arthritis precedes the appearance of skin lesions by several months to several years. Occasionally, joint symptoms and skin lesions appear simultaneously, observed in 21% of cases, or skin lesions appear first, occurring in 18% of cases [2]. Inflammation predominantly affects the interphalangeal joints, with reported involvement rates ranging from 76% to 97% [1,2,], occurring with comparable frequency in the proximal and distal interphalangeal joints [2,3]. During MRH, spontaneous remission of lesions may occur after an average of 7-8 years of disease duration, while in about 45% of cases the disease progresses to arthritis mutilans [2,3]. MRH may have a much more aggressive course and lead to a much greater degree of joint destruction and deformity, compared to rheumatoid arthritis (RA) [2].

In addition, single cases of involvement of internal organs have been described, including the heart and pericardium (leading to heart failure and pericardial effusion), the lungs and pleura (notably pleural effusion) [3], and the liver, kidneys, and thyroid [2,6].

One of the most frequently described concomitant autoimmune disease is Sjögren's syndrome. Additionally, there have been documented cases of RA, systemic sclerosis, systemic lupus erythematosus, thyroid disease, type 1 diabetes, primary biliary cirrhosis, juvenile idiopathic arthritis, myasthenia gravis and immune thrombocytopenic purpura [1]. To date, only one instance of a patient exhibiting both MRH and psoriasis [3], similar to our patient, has been recorded, rendering this association exceedingly rare. According to the literature, malignant tumors have been observed in 15-30% of patients, predominantly of epithelial origin [7].

The most frequently encountered types include lung, ovarian, stomach, and prostate cancers [8]. Furthermore, cases of concurrent malignant skin tumors, specifically melanoma, have also been documented [3]. In light of the prevalent co-occurrence of MRH with malignant tumors, it is proposed that MRH may signify a paraneoplastic syndrome [9].

Macrophages significantly influence the inflammatory reaction in MRH, though its etiology is unclear [1]. Pro-inflammatory cytokines like tumor necrosis factor α (TNF-α), interleukin 12 (IL-12), interleukin 6 (IL-6), and interleukin 1β (IL-1β) are overexpressed in skin lesions, along with increased serum levels of TNF-α, IL-6, interleukin 8 (IL-8), and IL-1β. In addition, a case of elevated serum level of monocyte chemoattractant protein-1 (MCP-1) was described, which decreased after treatment, suggesting its possible role in the recruitment of histiocytes and giant cells to the site of the inflammatory reaction [1]. In some patients, increased osteoclast activity and the ability of synovial macrophages to differentiate into osteoclasts were observed, possibly explaining successful bisphosphonate treatments [1]. A significant correlation between MRH and the occurrence of neoplastic processes and other autoimmune diseases has also been noted. However, no direct evidence for their involvement in the etiopathogenesis of MRH has been described to date [8].

The only certain confirmation of the diagnosis of MRH is a histopathological examination, which reveals infiltration of histiocytes and multinucleated giant cells with eosinophilic cytoplasm with a ground-glass appearance in the affected tissues. The immunohistochemical detection of infiltrating cells was positive for CD68, vimentin, and LCA (CD45), and negative for the Langerhans histiocyte markers S-100, CD1a and CD34 [2].

There is no clear treatment protocol for MRH, which is challenging. First-line treatments typically include methotrexate, glucocorticoids, or nonsteroidal anti-inflammatory drugs. Second-line therapeutic options mainly focus on immunosuppressants, with the most commonly used ones being TNF-α inhibitors. Switching to a different TNF-α inhibitor can be an effective alternative if the first-line medication proves ineffective [1]. Recent reports suggest that upadacitinib, a JAK inhibitor, may effectively

treat MRH. Upadacitinib can lower IL-6 levels mediated by JAK-1 in patients with MRH, thereby reducing inflammation. It has also been proposed that MRH should be treated as a tumor disease, with molecular-targeted therapy recommended when necessary [10].

Conclusion

Multicentric reticulohistiocytosis is an extremely rare disease that poses many diagnostic and therapeutic challenges. Nonspecific initial symptoms of arthritis and sporadic occurrence may lead to a delay in diagnosis. During differential diagnosis, MRH should be considered in patients with a history of autoimmune disease in whom joint symptoms have developed or worsened. The subsequent appearance of specific skin lesions facilitates the final diagnosis. Early effective therapy is crucial in preventing progression to arthritis mutilans. Further studies are necessary to understand the etiology of MRH and to determine an effective therapeutic regimen.

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