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Research Article

Dermatomyositis-Like Multicentric Reticulohistiocytosis: A Clinical Clue to Verify Underlying Malignancy

Vessel Kantardjiev[1], Boyana Beshanska-Pedersen[1], Elena Obreshkova[1], Valentina Broshtilova[1,2]*

[1]Department of Dermatology and Venereology, Military Medical Academy, Sofia, Bulgaria

[1,2] Department of Infectious Diseases, Parasitology and Dermato-venereology, Faculty of Medicine, Medical University "Prof. Dr Paraskev Stoyanov", Varna, Bulgaria

***Corresponding author:** Ndje Ndje Mireille, Clinical and Pathological Psychology, University of Yaounde I

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Abstract

Herein, an otherwise healthy 63-year-old Caucasian woman with a three month-history of progressive symmetrical swelling and of the fingers, lumbal and abdominal pain, proximal muscle weakness, and heliotropic rash resembling V- neck, histologically verified as multicentric reticulohistiocytosis (MRH), is presented. Multiple computer tomography scans failed to detect ovarian cancer despite elevated Ca 125, however, it was verified six months later by magnetic resonance investigation. Multicentric reticulohistocytosis (MRH) is a rare systematic disease that targets skin, mucoses and synovium, resulting in skin nodules, mucosal lesions and deforming painful mutilating polyarthritis. Twenty – five percent of all patients are associated with internal malignancies, hence, MRH paraneoplastic nature remains extremely controversial. Our case showed a peculiar dermatomyositis-like clinical subtype, which we consider suggestive for verification of an underlying malignancy.

Key words: multicentric reticulohistiocytosis; paraneoplastic syndrome

Introduction

Multicentric reticulohistocytosis (MRH) is first described by Weber and Freudenthal in 1937. Golz and Laymon coined the term MRH [1], while 15 years later Barrow et al. provided the first working definition of the non-Langerhans histiocytosis [2]. Approximately 300 cases of MRH, mostly in Western countries and Japan, are reported worldwide [3]. MRH is more common in females (2-3:1) [4] with mean presentation in the 4th and 5th decade. Anecdotal pediatric cases have also been described [5].

A MRH case, clinically presented with heliotropic erythema, mimicking dermatomyositis, in association with an underlying ovarian cancer is, herein, described.

Case report

An otherwise healthy 63-year-old woman presented with a three-month history of progressive swelling, stiffness of the fingers on both hands, lumbal and abdominal pain, and proximal muscle weakness. The patient reported weight loss, malaise and abdominal pain as first symptoms. On physical examination a heliotropic poikilodermic exanthema with peripheral telangiectasias were seen on her presternal area (Fig. 1).

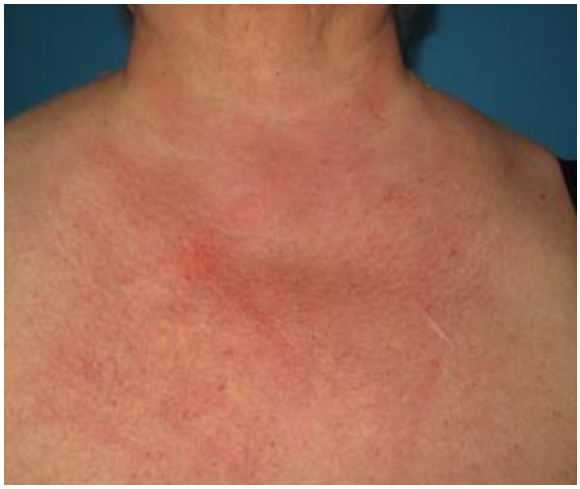

Fig. 1: Heliotropic presternal teleangiectatic erythema

Reddish-brown papules and nodules were regularly distributed on the dorsum of the fingers. Diffuse erythematous macules were noticeable on the abdominal wall. Coral beads around the nail matrix were also observed (Fig. 2).

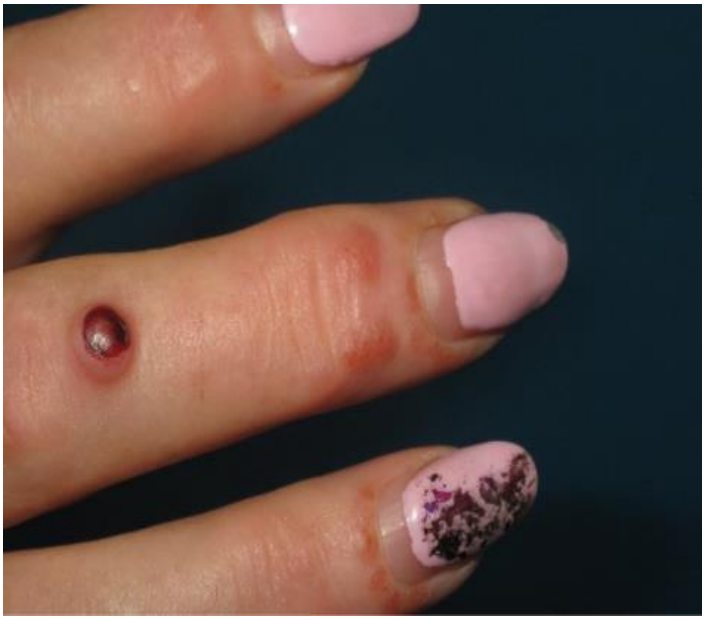

Fig. 2: Coral beads around the nail matrix – a pathognomic sign

The diagnostic presumption of dermatomyositis, based on heliotropic erythema, polyarthritis, and muscle weakness, was ruled out upon histological verification that showed hyperkeratosis, regular acanthosis, a dense infiltrate of histiocytes and multinuclear cells with abundant "ground glass" cytoplasm (Fig.3) with fine periodic acid-Schiff–positive granules and CD 68 positivity (Fig.4). The nuclei of the giant cells have been arranged aligned on the periphery or clustered in the center. The diagnosis of multinucleated reticulohistiocytosis was concluded.

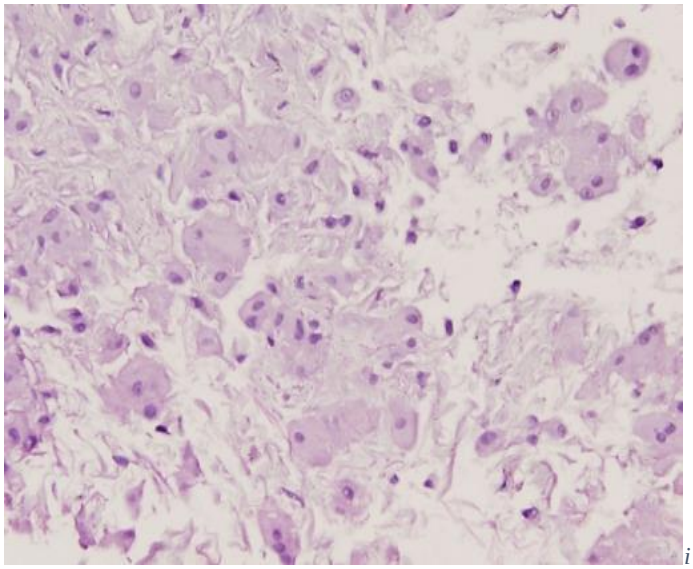

Fig. 3: Giant cells with "ground glass" cytoplasm (H&E, x 200)

A full body work-up ruled out infectious, immunological and metabolic conditions. Ultra sound and computer tomography investigations of chest, abdomen, pelvis and lungs showed no pathological changes.

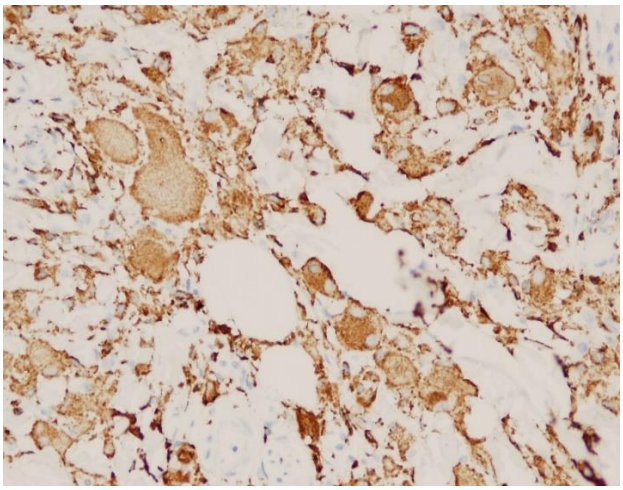

Fig. 4: CD 68-positive cells

The patient was started with a combined quadruple regimen of hydrocortisone 5mg daily, alendronate 70 mg weekly, methotrexate 7.5 mg weekly, and folic acid 10 mg weekly[22, 23]. Reduction of finger edema, alleviation of arthralgias and increased quality of life were registered at the first-month follow-up.

A persistent monitoring of CA 125 was performed during the next six months with no significant change in values. Several obstetric consultations were also done, none verifying an underlying malignancy. The third-month follow-up sonography and computer tomography scan were negative, too. At the six-month check-up the patient reported an abdominal pain. The third sonography susspected ovarian cancer, which was verified by magnetic resonance. A radical hysterectomy with wide lymph dissection was performed.

Discussion

MRH is a rare systematic disease that targets skin, mucoses and synovium, resulting in subcutaneous nodules, mucosal lesions and deforming painful mutilating polyarthritis [6]. The diagnosis is extremely challenging and based entirely on histopathological findings. No pathognomic clinical features exist, perhaps with the exception of coral beads around the nail matrix, which have been considered more specific [2,4]. The poikilodermic presternal erythema and heliotropic rash seen in our patient were suggestive of dermatomyositis. The dermatological symptoms corresponded well with symmetrical joint involvement and consumptive syndrome. Only the histological verification was able to conclude MRH, thus proving the observations of other authors who outline dermatomyositis-like changes in MRH as a specific clinical subtype [7].

MRH pathogenesis remains obscure. It is considered a reactive proliferation of tissue macrophages due to unknown and hardly-to-differentiated triggers. TNF alpha and other inflammatory cytokines are highly expressed in the synovium and synovial fluid of affected joints in patients with MRH [8]. Quantative amounts of pro-inflammatory cytokines are elevated in the synovial fluid, among them- TNF-alpha, IL6, IL12, and IL1-beta and these findings have important implications from a therapeutic standpoint, as also supported by the reported benefit of TNF-

alpha inhibitors [9]. Pro-inflammatory cytokines are likely produced by synovial fluid macrophages and may represent a common mechanism with rheumatoid arthritis. More recent data support that synovial fluid macrophages may differentiate into osteoclasts following RANKL pathway activation or macrophage colony stimulating factor [10].

Paraneoplastic nature of the disease is highly controversial. The malignancy-associated MRH varies between 25-31%.[11] Most common underlying neoplasms are: pancreatic adenocarcinoma, squamous cell carcinoma of the lung, metastatic melanoma, papillary serous carcinoma of endometrium, recurrent breast carcinoma [12]. By 73% of the patients MRH diagnosis preceded the associated tumor [13]. Herein, we speculate on the dermatomyositis-like peculiar MRH clinical presentation as a validator of the paraneoplastic nature of the disease. We would like to propose dermatomyositis-like MRH as a prognostic clue for an underlying malignancy.

No comprehensive therapeutic approach has been recently worked out. Although MRH has the tendency to self-resolve in an average of 8 years, treatment must be started early to avoid sequelae, mainly in joints with severe deformities and daily life activity impairment [14]. The latest guidelines proposed methotrexate as the most effective initial disease-modifying antirheumatic drugs [15]. It controls arthritis symptoms in 28 % cases and skin lesions in 38 %. Leflunomide [16] and azathioprine [17] are considered in cases contraindicative to methotrexate. Alendronate has a protective role on the bones and prevents histiocytes to differentiate in osteoclasts. It is beneficial for the patient to start alendronate even before a mutilating arthritis is present [18]. Cyclophosphamide was found to be of significant benefit with 20 % of cases with complete arthritis resolution and 1/3 cases of skin lesions. [2] Hydroxychloroquine and sulfasalazine show no significant benefit but may be used in combined treatment regimens. Anti TNFα blockers are also considered beneficial [5]. Successful treatment with anti-IL1 inhibitors and interleukin-6 receptor (IL-6R) is also reported [19]. Paraneoplastic cases require concomitant control on malignant process by using radical surgery and adjuvant radio- and chemotherapy [12]. New treatments for osteoporosis targeting cathepsin K are being developed [20], and the enhanced expression of this mediator by fibroblasts of patients with rheumatoid arthritis and in MRH synovial fluids may provide novel treatment approach [18].

We have followed the guidelines to use a quadruple combination of corticosteroid, methotrexate, folic acid and alendronate,once the diagnosis was proven on histology.

Conclusion

MRH is a challenging diagnosis with peculiar clinical and histopathological features. The very few cases published worldwide do not give enough evidence of the scientific community to build a reasonable pathogenetic concept and sensible hypothesis of the common disease associations. Our clinical observation proved the already-described correlation of dermatomyositis-like MRH clinical subtype with an underlying malignancy. Therefore, we would like to suggest MRH dermatomyositis-like clinical subtype as a validator of the paraneoplastic nature of the disease.

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