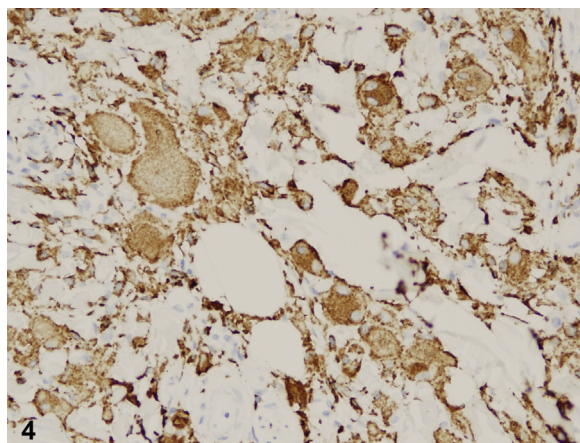
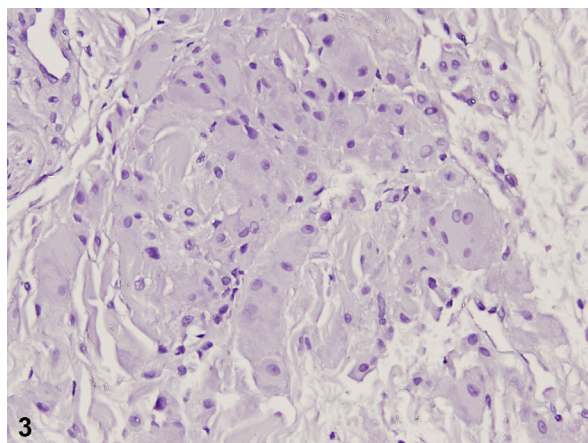


Reddish-brown papules and nodules on the hands



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Key words: dermatomyositis; multicentric reticulohistiocytosis; rheumatoid arthritis.



An otherwise healthy 63-year-old woman presented with a 3-month history of weight loss, malaise, and abdominal pain as first symptoms, followed by back pain, proximal muscle weakness, and symmetrical painful decapacitating arthritis of the small joints of the hands. On physical examination, reddish-brown papules and nodules were found on the dorsum of the fingers, some overlying the periungual area (Fig 1). A photo-distributed pink, violaceous erythema with telangiectasias was noticeable on the neck and anterior chest (Fig 2). Ovarian cancer was found during the follow-up period. Punch biopsy of a nodule was performed (Figs 3 and 4).

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Question 1: What is the most likely clinical diagnosis?

- A. Subcutaneous granuloma annulares (SGA)
- B. Erythema elevatum diutinum
- C. Rheumatoid arthritis (RA)
- D. Multicentric reticulohistiocytosis (MRH)
- E. Dermatomyositis (DM)

Answers:

A. SGA — Incorrect. SGA is an uncommon variant of granuloma annulare seen almost exclusively in young children.¹ It is characterized by the appearance of subcutaneous firm nodules, varying in size between 0.5 and 4 cm, localized on the pretibial area and on the ankles, dorsum of the feet, buttocks, hands, and scalp. The lesions usually regress after several years. Histologic examination shows a palisading granuloma.

B. Erythema elevatum diutinum — Incorrect. Erythema elevatum diutinum is a rare, localized variant of leukocytoclastic vasculitis.² It is characterized by persistent firm, red, purple, brown, or yellow nodules measuring up to about 1 cm in diameter or oval elevated plaques 5 to 6 cm in diameter. The lesions are most frequently located on the extensor surfaces of the joints. The disease is chronic and progressive, with resolution occurring within 5 to 10 years. An association with paraproteinemia is frequently present, often of the IgA subtype. An underlying myelodysplastic syndrome or a hematologic malignancy has been found in some patients. Histologic examination shows leukocytoclastic vasculitis in early lesions and granulation tissues and fibrous scarring in older lesions.

C. RA — Incorrect. RA is an autoimmune disorder that primarily affects the joints. Rheumatoid nodules are subcutaneous lesions that develop on the sites of trauma or pressure points in approximately 30% of adult patients. Histologically, rheumatoid nodules exhibit a palisading granulomatous reaction with extensive necrobiosis and deposition of fibrin in the center of the nodule.

D. MRH — Correct. MRH is a rare, non-Langerhans-cell histiocytosis, characterized by brown papulonodular cutaneous eruptions and destructive arthritis. Eleven percent of patients have skin manifestations resembling those of DM: Gottron's papules, heliotrope rash, V-neck sign, and shawl sign. Pruritus is an important clue that distinguishes MRH-like DM from classic DM.³ Histopathologic

examination of mature skin lesions of MRH demonstrates histiocytes and multinucleated giant cells with pale, fine, granular "ground-glass" eosinophilic cytoplasm positive for CD68. Biopsy specimens from erythema on the chest show mild liquefaction degeneration and perivascular lymphocyte infiltration. Malignancy is the most common condition associated with MRH (in 25% to 31% of cases).

E. DM — Incorrect. DM is an uncommon inflammatory disease characterized by the triad of distinctive skin rash, muscle weakness, and inflammatory myopathy. Cutaneous findings include heliotrope rash and erythema on the face, anterior neck, and upper chest (V-neck sign), upper back (shawl sign), and extensor surfaces of the limbs and dorsal aspects of the hands and fingers. Other findings are erythematous papules over the metacarpophalangeal joints (Gottron's sign), periungual erythema, telangiectasias, splinter hemorrhages, and dilated capillary loops. Polymyositis mainly presents with symmetrical proximal (limb girdle) muscle weakness and dysphagia, associated with malignancy. Adult patients with DM have an elevated risk of malignancy (from 9% to 42%). Pruritus is often a debilitating feature of DM. Elevated levels of interleukin 31 have been implicated in DM-associated itch. Histopathologic examination shows vacuolar changes of basal keratinocytes, dermal mucin accumulation, and a mild to moderate dermal mononuclear inflammatory cell infiltrate. In some instances, there is considerable histologic overlap with lupus erythematosus. The muscle biopsy is diagnostic, with perifascicular atrophy as the main clue.

Question 2: Which of the following is a reported treatment option for MRH?

- A. Gold salts (sodium aurothiomalate)
- B. Chlorambucil
- C. Sulfasalazine
- D. Methotrexate
- E. Minocycline

Answers:

A. Gold salts — Incorrect. Patients with MRH and arthritis reported no response to gold salts.⁴ Gold salts are indicated for the treatment of RA unresponsive to conventional chemotherapy. The anti-arthritic mechanism of action of gold salts is unknown. One of the most popular hypotheses

suggests that the accumulation of gold by macrophages inhibits both phagocytosis and the activities of lysosomal enzymes, and in advanced RA, gold salts may prevent further damage to affected joints.

B. Chlorambucil — Incorrect. Chlorambucil worsens the disease.⁴ Short-term, low-dose chlorambucil has a great effect on generalized granuloma annulare, but because of its bone marrow suppression other treatments are preferred.

C. Sulfasalazine — Incorrect. Sulfasalazine worsens both arthritis and skin lesions.⁴ It is a type of drug known as a disease-modifying antirheumatic drug, and it is considered a first-line treatment for RA.

D. Methotrexate — Correct. Methotrexate is the most effective treatment. It controls both arthritis and skin lesions. It is the first choice of treatment.⁴

E. Minocycline — Incorrect. There is no response to minocycline.⁴ It has been reported that tetracyclines can exert a variety of biological actions that are independent of their antimicrobial activity, including anti-inflammatory and antiapoptotic activities and inhibition of proteolysis, angiogenesis, and tumor metastasis. Recently, minocycline has been used to treat various diseases with an inflammatory basis. It has been beneficial in patients with RA.

Question 3: What are the most common conditions associated with MRH?

- A. Granuloma faciale
- B. Periodontitis
- C. Diabetes mellitus type 1
- D. Malignancy
- E. Thyroid dysfunction

Answers:

A. Granuloma faciale — Incorrect. Granuloma faciale is an uncommon benign chronic skin disease of unknown origin, characterized by one or several asymptomatic, soft, reddish-brown, slowly enlarging papules or plaques, almost always on the face. The disease mimics many other dermatoses. The histologic findings are diagnostic: dense polymorphous inflammatory infiltrate, usually with eosinophil predominance and some evidence of vasculitis. However, the histologic features of the

late lesions of granuloma annulare and erythema elevatum diutinum often overlap, and similar features are found in chronic fibrosing vasculitis.

B. Periodontitis — Incorrect. An association between periodontitis and RA is hypothesized to lead to enhanced generation of RA-related autoantibodies. Oral bacteria invading the blood may also contribute to chronic inflammatory responses and generation of autoantibodies.⁵

C. Diabetes mellitus type 1 — Incorrect. Diabetes mellitus is the most common association in granuloma annulare patients.

D. Malignancy — Correct. Over 21% of MRH cases were associated with malignancy: most commonly breast cancer, ovarian adenocarcinoma, ovarian neuroectodermal tumor, cutaneous squamous cell carcinoma, melanoma, papillary serous endometrial cancer, nasopharyngeal cancer, and hepatocellular carcinoma.⁴

E. Thyroid dysfunction — Incorrect. Thyroid dysfunction is not associated with MRH. The association with granuloma annulare is still to be shown by further surveys.

Abbreviations used:

DM: dermatomyositis

MRH: multicentric reticulohistiocytosis

RA: rheumatoid arthritis

SGA: subcutaneous granuloma annulare

Conflicts of interest

None disclosed.

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