

Reticular Erythematous Mucinosis: A Rare Cutaneous Mucinosis

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ABSTRACT Reticular erythematous mucinosis (REM) is a rare form of primary cutaneous mucinosis, most often involving the midline of the upper chest or back in middle-aged women. REM bears clinical and histopathologic resemblance to lupus erythematosus tumidus (LET), dermatomyositis, scleredema, and lichen myxedematosus. Early recognition and diagnosis of REM is particularly relevant to exclude the abovementioned diseases, as REM is more benign and has fewer systemic consequences.

KEY WORDS: reticular erythematous mucinosis, lupus erythematous tumidus, scleredema, dermatomyositis, lichen myxedematosus, papular mucinosis

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INTRODUCTION

The cutaneous mucinoses are a diverse group of disorders in which elevated levels of mucin are found in the skin, predominantly in the dermis (1). The primary cutaneous mucinoses are characterized by mucin deposition as the major histological feature, and include scleromyxedema, scleredema, and lichen myxedematosus (papular mucinosis) among others (1). Secondary mucinoses are disorders in which mucin deposition is an additional finding, and include lupus erythematous, dermatomyositis and granuloma annulare (1).

Reticular erythematous mucinosis (REM), first described by Steigleder in 1974, is a rare form of primary cutaneous mucinosis, most often involving the midline of the upper chest or back in middle-aged women (2,3). Within the heterogeneous group of disorders of cutaneous mucinosis, REM bears clinical and histo-

pathologic resemblance to lupus erythematosus tumidus (LET), dermatomyositis, scleredema, and papular mucinosis. However, recent evidence supports the recognition of REM as a distinct entity, based on its distinctive clinical and histologic features of this disorder. Therefore, early recognition and diagnosis of REM are particularly relevant, as it excludes lupus, scleredema, papular mucinosis or dermatomyositis. REM is more benign and has fewer systemic consequences than the abovementioned diseases.

EPIDEMIOLOGY OF REM

REM is also known as plaque-like cutaneous mucinosis or midline mucinosis (3,4). It usually is first evident as a non-scaly eruption of erythematous macules and papules in a reticulated pattern most commonly over the midline of the chest (3). In rare

cases, REM may also be evident on other sites such as the face, legs, arms, and abdomen (5). Most often, patients are women in the third and fourth decades of life. They often have a relapsing and remitting course, with the disease limited to the skin (3,4).

Although the etiology is unknown, fibroblasts of patients with REM have an abnormal response to exogenous IL-1b (6). In addition, tubuloreticular inclusions have been detected in endothelial cells and pericytes within the skin lesions (6). The disease is exacerbated by menses, contraceptives, and pregnancy, suggesting a possible hormonal basis. Solar exposure can flare it too, or in some cases improve the disease course. It may be associated with smoking (7), lupus erythematosus, diabetes mellitus, myxedema, hypothyroidism, Hashimoto's thyroiditis, thrombocytopenia, monoclonal gammopathy, HIV infection, breast cancer, and colon cancer (3,4). Immunologic disturbances and viral infections have also been postulated to be linked with the induction of REM syndrome (7).

Fühler *et al.* (8) described monozygotic female twins who both presented with REM at almost the same time in the same location after UV exposure. Familial manifestations of REM syndrome are rare; an association with a distinct HLA constellation has not been proven. However, the almost simultaneous appearance of cutaneous lesions by light provocation at identical sites in these twin sisters suggests a genetic predisposition.

Atci *et al.* delineated REM involving a mastectomy scar, the upper chest and the midline of the back. This patient then underwent a mammary reconstruction involving an abdominal skin flap. The abdominal skin flap was lesion-free prior to the reconstruction; however, after the reconstruction, the abdominal skin flap demonstrated appearance of REM. As such, REM should be included in the differential diagnosis of persistent erythematous patches occurring on scar sites.

Differential Diagnosis for REM

Clinical diagnosis of REM is by exclusion, facilitated by clinical, histopathologic, and laboratory correlation to rule out lupus erythematosus tumidus (LET), papular mucinosis (PM), dermatomyositis (DM) and scleredema (Table 1). Clinically, REM, LET, and DM can show erythematous plaque-like lesions with significant lack of serologic abnormalities; however, the shape and distribution of lesions aid in distinction. REM's principle lesion is more often a papule than a patch or plaque. Its reticulated pattern is distinct and most often involves the skin of chest, less commonly the upper back, with variable photosensitivity.

Dermatomyositis (DM)

The primary skin lesions of DM are erythematous to violaceous papules and plaques, most often located symmetrically on the extensor dorsal aspects of the metacarpophalangeal and interphalangeal joints (Gottron's papules), with the second most common distribution being a heliotrope eruption of the upper eyelids. Both of these skin findings are pathognomonic for DM (9). Less commonly, DM may present with a maculopapular rash that may be related to photosensitivity, which can mimic the skin findings seen in REM patients. Other skin findings in DM include photo-distributed poikiloderma (neck, shawl), scalp dermatitis, nailfold telangiectasias, violaceous plaques over the knees and elbows, calcinosis cutis (more in juvenile variant), and mechanic hands (ragged cuticles, hyperkeratosis, scaling, and fissuring of distal fingers) (9). The muscular involvement is clinically characterized by symmetrical, proximal, progressive muscle weakness (9). It is important to note that muscular involvement is often seen in DM patients, and has not been associated with REM.

A study by Edward *et al.* (10) found that the mucinous lesions may be caused by the presence of certain serum-derived factors. This work demonstrated that serum from patients with DM stimulates both sulphated glycosaminoglycan and hyaluronic acid synthesis by fibroblasts from both control and involved skin. In contrast, the fibroblasts from patients with DM show similar levels of GAG synthesis as control fibroblasts in the presence of a control serum. These results suggest that these fibroblasts are not activated, nor contain a population of cells that overexpress GAGs. DM is frequently associated with the presence of an underlying malignancy (11). As DM is frequently associated with the presence of an underlying malignancy, it is possible that the tumor may be releasing factors into the serum to promote the development of the characteristic mucinous lesions.

DM is primarily treated with steroids, though hydroxychloroquine, methotrexate, and azathioprine may also be used (9). Maugers *et al.* (12) studied the long-term prognosis of patients with DM and found that survival rates were 82.6% at 1 year, 73.9% at 2.66 years, 7% at 5 years and 55.4% at 9 years. The main prognostic factors were old age, cancer, pulmonary interstitial fibrosis and asthenia-anorexia.

Lupus erythematosus tumidus (LET)

LET is commonly first evident with erythematous, urticarial-like single or multiple plaques with no surface changes such as follicular plugging. They involve sun-exposed areas, especially the face, upper



Table 1. Comparing REM, LET, DM, scleredema, and LM

	REM	LET	DM	Scleredema	LM
History	Women in 3 rd or 4 th decade of life; exacerbated by oral contraceptives, menses, and pregnancy	Associated with smoking - males and females equally affected	Underlying malignancy, can also present with myositis	Underlying etiology including recent streptococcal infection, hyperparathyroidism, Sjögren syndrome, rheumatoid arthritis, malignant insulinoma, multiple myeloma, HIV infection, diabetes mellitus	Adults between the ages of 30 and 80 years with no race or gender predominance; underlying monoclonal gammopathy or malignancy
Physical	Non-scaly eruption of erythematous macules and papules in a reticulated pattern most commonly over the midline of the chest	Erythematous to violaceous plaques or nodules, with or without an annular pattern on sun-exposed areas that are non-scarring	Erythematous to violaceous papules and plaques, most often located symmetrically on the extensor dorsal aspects of the metacarpophalangeal and interphalangeal joints, with the second most common distribution being a heliotrope eruption of the upper eyelids	Firm and woody plaques, diffuse, symmetric, non-pitting skin induration; classically affects the upper back and posterior neck	Normochromic or erythematous papules, ranging from 1 mm to 4 mm. The papules are firm and waxy and are symmetrically arranged, primarily on the back of the hands and fingers, the extensor surface of the arms, the face, the upper torso, and the legs
Pathology biopsy findings/Labs	More superficial inflammatory infiltrate and more superficial mucin deposition, as well as less frequent immunoglobulin and complement deposition along the DEJ as compared to LET	Perivascular and periadnexal lymphocytic infiltration with interstitial mucin deposition, scattered neutrophils, no epidermal involvement; ANA in 10%, anti-Ro/SSA and anti-La/SSB antibodies in 5% of patients	Epidermal atrophy; membrane attack complexes at the dermal-epidermal junction (DEJ) as well as increased CD4 positivity when compared to LET	Epidermis is also typically uninvolved, with the dermis being up to four times thicker than normal due to enlarged collagen bundles in deep reticular dermis with wide, clear, mucin-filled spaces between them	Specimens from extracutaneous sites may demonstrate mucin deposition in the subendothelial space and in the interstitium of the kidney, lungs, pancreas, adrenal glands and nerves
Treatments	Anti-malarials, tacrolimus, topical tacrolimus, oral antihistamines, tetracycline, cyclosporine, UVB irradiation, UVA1 irradiation, pulsed dye laser, and topical and systemic corticosteroids	Anti-malarials effective in 90% of cases; local corticosteroids	Steroids, hydroxychloroquine, methotrexate, azathioprine	Phototherapy, systemic corticosteroids, methotrexate, thalidomide, cyclosporine, plasmapheresis, radiation, IVIg	Cyclophosphamide, intralesional infiltration with hyaluronidase and triamcinolone, CO2 laser, methotrexate, cyclosporine, radiotherapy, thalidomide, plasmapheresis, systemic corticosteroid, chloroquine, IVIg, retinoids, PUVA
Prognosis	The most favorable prognosis	Favorable prognosis, systemic involvement rare	~80% survival at 1 year, ~55% survival 9 years	Type 2 and Type 3 have poor prognosis, with chronic progressive courses and systemic complications	Progressive and disabling

back, neck, extensor aspects of the arms, and shoulders, and typically spare the knuckles, inner aspect of the arms, and axilla. They do not usually occur below the waist. LET can sometimes cause photosensitivity, and, as with REM, LET was also found to be highly associated with smoking (14). Although joint symptoms can occur temporarily, no signs of inflammatory joint disease is usually evident (13). A study by Kuhn *et al.* found that further systemic manifestations including renal, central nervous system, or lung involvement, had not manifested in any of the 40 study patients with LET for 15 years. Their study also showed that 55% of the affected patients were male. ANA was positive in 10% of the patients; anti-Ro/SSA and anti-La/SSB antibodies were present in 5% of patients. Patients with LET are usually antimalarial responsive; the use of topical or intralesional corticosteroids as adjunctive therapies may be beneficial (15).

SCLEREDEMA

Scleredema presents as diffuse, symmetric, non-pitting skin induration caused by dermal glycosaminoglycan deposits (16). It classically affects the upper back and posterior neck, causing skin tightness, and decreased range of motion. The affected areas are firm and woody plaques, sometimes slightly red or brown and often with a 'peau d'orange' (orange-skin) appearance. Scleredema occurs in individuals of all ages, with more than 50% of patients aged under 20 years. Three types of scleredema have been described according to their association with underlying conditions. Type 1 (the classic 'Buschke' type, 55% of cases) usually follows a febrile infection (especially streptococcal or viral respiratory tract infection) and affects mainly children (16). Type 2 (25%) is associated with paraproteinemia including monoclonal gammopathy, multiple myeloma and amyloidosis. Type 3 (20%) is associated with diabetes mellitus. Other associated diseases include primary hyperparathyroidism, rheumatoid arthritis, ankylosing spondylitis, Sjögren's syndrome, dermatomyositis, Waldenström's macroglobulinemia, and IgA deficiency. Concomitant neoplasms have been reported, such as malignant insulinoma, gall bladder carcinoma, carcinoid tumor and adrenocorticotrophic hormone-producing pituitary tumour (17). In types 1 and 2 scleredema, women are affected almost twice as frequently as men. In contrast, in type 3 scleredema, the male- to-female ratio is considered to be 10:1 (16).

The treatment of scleredema remains a challenge, with therapeutic options including phototherapy, systemic corticosteroids, methotrexate, thalidomide, cyclosporine, plasmapheresis, and radiation (18). Kennemer *et al.* (17) found that IVIg was effective in

treating scleredema with a longer duration of treatment leading to a slower rate of relapse. However, no treatment has been shown to be consistently effective in large numbers of patients. Type 1 scleredema associated with a preceding infection is characterized by a good prognosis and even spontaneous resolution (17). Type 2 and Type 3 have poor prognosis, and may occasionally have chronic progressive courses and systemic complications.

LICHEN MYXEDEMATOSUS

Lichen myxedematosus (LM) is characterized by fibroblast proliferation and mucin deposition in the dermis and is classified into two subtypes based upon severity. The milder, more localized type is called "papular mucinosis" and is also known as "lichen myxedematosus". The other type is a severe, generalized more sclerotic and diffused form known as scleromyxedema. The localized form has a more favorable course compared to scleromyxedema, which can involve other organs and is sometimes fatal (16). The disease usually affects adults between the ages of 30 and 80 years with no race or gender predominance.

Cutaneous findings include erythematous papules, in diameter from 1 mm to 4 mm (19). The papules are firm and waxy and are symmetrically arranged, primarily on the back of the hands and fingers, the extensor surface of the arms, the face, the upper torso, and the legs. Scalp and mucosae are not affected. They may coalesce, resulting in widespread induration of the skin, eventually leading to leonine facies and microstomia. Erythema, edema and a brownish discoloration may be seen in the involved areas; pruritus is also common (16). Eyebrow, axillary and pubic hair may be sparse in patients with scleromyxedema. The pathogenesis of scleromyxedema is unknown. The main hypothesis is that circulating cytokines such as IL-1, TNF-alpha and TGF-beta, which are known to stimulate glycosaminoglycan synthesis and fibroblast proliferation in the skin, are involved. The condition is usually associated with a monoclonal gammopathy. Scleromyxedema may also be involved with an underlying neoplasm (20).

In a multicenter retrospective study of 30 patients with scleromyxedema, the most common extracutaneous manifestations were neurologic abnormalities (30%), rheumatologic abnormalities (25%) and cardiac abnormalities (22% of patients) (21). The dermatoneuro syndrome is a rare and potentially lethal acute neurologic complication characterized by fever, confusion, dysarthria, lethargy, convulsions and coma (21,22).

Scleromyxedema is a disease with an unpredictable but usually progressive and disabling course. The alkylating agent melphalan has been considered a first-line treatment, but has limited use due to its side effects (19). Other treatment options include cyclophosphamide, intralesional infiltration with hyaluronidase and triamcinolone, CO2 laser, methotrexate, cyclosporine, radiotherapy, thalidomide, plasmapheresis, 2'-deoxyadenosine (2-CD), systemic corticosteroid, chloroquine, intravenous immunoglobulin, retinoids, chemotherapeutic agents, and PUVA (19).

COMPARING HISTOLOGY OF REM, DM, LET, SCLEREDEMA, AND LM

Histologically, subtle features can also help to identify REM as a distinct entity, while helping to differentiate its diagnosis from that of DM or LET. All three diseases show minimal epidermal change with dermal perivascular lymphocytic infiltrate and increased dermal mucin deposition. Distinguishing features of DM include membrane attack complexes at the dermal-epidermal junction (DEJ) as well as increased CD4 positivity when compared to LET (23). A recent study which analyzed features of LET and REM identified differences in the type and location of inflammatory infiltrate, mucin deposition, and immunoreactant deposition at the DEJ, helping to justify the distinction between the two and help guide diagnosis (24). In this retrospective and prospective study of 25 patients with REM, Cinotti and colleagues (24) observed a more prominent and deeper dermal inflammatory infiltrate and deeper mucin deposition in LET when compared with REM. A tropism for adnexa in LET was also noted. REM patients demonstrated both a more superficial inflammatory infiltrate and more superficial mucin deposition, as well as less frequent immunoglobulin and complement deposition along the DEJ as compared to LET. In scleredema, the epidermis is also typically uninvolved, with the dermis being up to four times thicker than normal due to enlarged collagen bundles in deep reticular dermis with wide, clear, mucin-filled spaces between them. In LM the cutaneous biopsy shows an increase in mucin, with an increase in fibroblasts, and increased fibrosis. The extracutaneous LM histology sites may demonstrate mucin deposition in the subendothelial space and in the interstitium of the kidney, lungs, pancreas, adrenal glands and nerves. Lymph node involvement with infiltration by numerous fibroblasts surrounded by mucin and collagen deposits has also been observed.

Management of REM

Sun avoidance and protection are recommended as a first line therapy. Conventional antimalarial drugs like chloroquine, and hydroxychloroquine should be considered as a second option (7). Quinacrine may be used in patients that are allergic, or have certain eye diseases (25). Other treatments employed with variable results include topical tacrolimus, oral antihistamines, tetracycline, cyclosporine, UVB irradiation, UVA1 irradiation (26), pulsed dye laser (27), and topical and systemic corticosteroids. It is important to note that REM is usually a self-limiting disease and may clear spontaneously, even after many years (1).

CONCLUSION

In summary, REM should be considered in the differential diagnosis of any non-scaly erythematous maculopapular eruptions on the upper chest and upper back. Though it may present similarly to DM, LET, scleredema, and lichen myxedematosus, REM should be considered as a distinct entity. Entertaining the diagnosis of REM is particularly relevant for those patients who may have lupus, scleredema, or dermatomyositis in their list of differential diagnoses, as REM is more benign and lacks systemic consequences. Furthermore, the prognosis for patients with REM is excellent, certainly favorable when compared to these other diseases. Clinicopathologic correlation is pivotal.

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References:

1. Rongioletti F, Rebora A. Cutaneous mucinosis: microscopic criteria for diagnosis. *Am J Dermatopathol.* 2001;23:257-67.
2. Steigleder GK, Gartmann H, Linker U. REM syndrome: reticular erythematous mucinosis (round-cell erythematosis), a new entity?. *Br J Dermatol.* 1974;91:191-9.
3. Bologna JL, Jorizzo JL. *Dermatology.* 2nd ed. Elsevier Limited. 2012; p. 618.
4. James WD, Elston D, Berger T, Neuhaus I. *Andrews' Diseases of the skin.* 11th Elsevier Limited. 2011; p. 185-186.
5. Atci T, Ekinçi AP, Buyukbabani N, Baykal C. Reticular erythematous mucinosis on a mastectomy scar and relapse after mammary reconstruction. *J Eur Acad Dermatol Venereol.* 2017;31:e13-e15.

6. Izumi T, Tajima S, Harada R, Nishikawa T. Reticular erythematous mucinosis syndrome: glycosaminoglycan synthesis by fibroblasts and abnormal response to interleukin-1 β . *Dermatology*. 1996;192:41-5.
7. Kreuter A, Scola N, Tigges C, Altmeyer P, Gambichler T. Clinical features and efficacy of antimalarial treatment for reticular erythematous mucinosis: a case series of 11 patients. *Arch Dermatol*. 2011;147:710-5.
8. Fühler M, Ottmann K, Tronnier M. Reticular erythematous mucinosis-(REM syndrome) in twins. *J Dtsch Dermatol Ges*. 2009;7:968-70.
9. Del Pozo J, Almagro M, Martínez W, Yebra-Pimentel MT, García-Silva J, Peña-Penabad C, Fonseca E. Dermatomyositis and mucinosis. *Int J Dermatol*. 2001; 40:120-4.
10. Edward M, Fitzgerald L, Thind C, Leman J, Burden AD. Cutaneous mucinosis associated with dermatomyositis and nephrogenic fibrosing dermopathy: fibroblast hyaluronan synthesis and the effect of patient serum. *Br J Dermatol*. 2007;156:473-9.
11. Leow YH, Goh CL. Malignancy in adult dermatomyositis. *Int J Dermatol*. 1997;36:904-7.
12. Maugars YM, Berthelot JM, Abbas AA, Mussini JM, Nguyen JM, Prost AM. Long-term prognosis of 69 patients with dermatomyositis or polymyositis. *Clin Exp Rheumatol*. 1996;14:263-74.
13. Kuhn A, Richter-Hintz D, Oslislo C, Ruzicka T, Megahed M, Lehmann P. Lupus erythematosus tumidus: a neglected subset of cutaneous lupus erythematosus: report of 40 cases. *Arch Dermatol*. 2000;136:1033-41.
14. Böckle BC, Sepp NT. Smoking is highly associated with discoid lupus erythematosus and lupus erythematosus tumidus: analysis of 405 patients. *Lupus*. 2015;24:669-74.
15. Bakardzhiev I, Chokoeva AA, Krasnaliev I, Tana C, Wollina U, Lotti T, Tchernev G. Unilateral unique Lupus tumidus: pathogenetic mystery and diagnostic problem. *Wien Med Wochenschr* 2016;166:250-3.
16. Knobler R, Moizadeh P, Hunzelmann N, Kreuter A, Cozzio A, Mouthon L, Cutolo M, Rongioletti F, Denton CP, Rudnicka L, Frasin LA. European dermatology forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 2: Scleromyxedema, scleredema and nephrogenic systemic fibrosis. *J Eur Acad Dermatol Venereol*. 2017;31:1581-94.
17. Kennemer C, Pavlidakey P, Sami N. Successful treatment with IVIg therapy of diabetes-associated scleredema severe progressive case and review of the literature. *Dermatol Ther*. 2017; 30. <https://doi.org/10.1111/dth.12504>
18. Namas R, Ashraf A. Scleredema of Buschke. *Eur J Rheumatol*. 2016;3:191.
19. Rebellato PR, Carbonar MB, Tabuti NI, Rastelli GJ. Case for diagnosis. Lichen myxedematosus. *An Bras Dermatol*. 2016;91:842-3.
20. Oh SJ, Oh SH, Jun JY, Park JH, Lee JH, Lee DY, Lee JH, Yang JM. Paraneoplastic atypical scleromyxedema with advanced gastric cancer. *JAAD Case Rep*. 2017;3:376.
21. Rongioletti F, Merlo G, Cinotti E, Fausti V, Cozzani E, Cribier B, Metze D, Calonje E, Kanitakis J, Kempf W, Stefanato CM. Scleromyxedema: a multicenter study of characteristics, comorbidities, course, and therapy in 30 patients. *J Am Acad Dermatol*. 2013;69:66-72.
22. Gonzalez J, Palangio M, Schwartz J, Klainer AS, Bisaccia E. Scleromyxedema with dermato-neuro syndrome. *J Am Acad Dermatol*. 2000;42:927-8.
23. Smith ES, Hallman JR, DeLuca AM, Goldenberg G, Jorizzo JL, Sanguenza OP. Dermatomyositis: a clinicopathological study of 40 patients. *Am J Dermatopathol*. 2009;31:61-7.
24. Cinotti E, Merlo V, Kempf W, Carli C, Kanitakis J, Parodi A, Rongioletti F. Reticular erythematous mucinosis: histopathological and immunohistochemical features of 25 patients compared with 25 cases of lupus erythematosus tumidus. *J Eur Acad Dermatol Venereol*. 2015;29:689-97.
25. Susok L, Kreuter A. Complete Clearance of Reticular Erythematous Mucinosis With Quinacrine Monotherapy. *Arch Dermatol*. 2012;148:768-9.
26. Meewes C, Henrich A, Krieg T, Hunzelmann N. Treatment of reticular erythematous mucinosis with UV-A1 radiation. *Arch Dermatol*. 2004;140:660-2.
27. Greve B, Raulin C. Treating REM syndrome with the pulsed dye laser. *Lasers Surg Med*. 2001;29:248-51.

