Morphea associated with primary biliary cirrhosis and Waldenstrom macroglobulinemia: Response to rituximab

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INTRODUCTION

Overlap exists between limited systemic sclerosis and primary biliary cirrhosis (PBC); however, rare case reports document an association between morphea and PBC.[1] Moreover, scleroderma-like tissue reactions are described in both solid-organ malignancies and plasma cell dyscrasias[2]; yet only 1 case report details an association between morphea and Waldenstrom macroglobulinemia (WM).[3] Here we describe a patient with PBC, WM, and recalcitrant morphea who responded to bendamustine-rituximab chemotherapy. Maintenance rituximab monotherapy (375 mg/m^2 every 3 months) was required to prevent flares of her skin disease.

Abbreviations used:

PBC: primary biliary cirrhosis
WM: Waldenstrom macroglobulinemia

CASE

A 54-year-old woman was referred for recalcitrant biopsy-confirmed morphea. She did not respond to treatment with potent topical steroids, tacrolimus 0.1% ointment, narrow-band ultraviolet B phototherapy, prednisone, hydroxychloroquine, and methotrexate. Medical history and autoimmune review of systems were noncontributory.

The patient presented in moderate distress caused by restricted chest expansion and shortness of breath. Indurated, shiny, flesh-colored plaques were noted on her left breast, lower abdomen, flanks, midback, bilateral inguinal regions, and thighs (Fig 1). Nail fold capillaroscopy examination was unremarkable.

All indicated laboratory test results and diagnostic imaging findings were within normal limits except for the following: elevated liver enzymes (aspartate transaminase, 66 U/L; alanine transaminase, 86 U/L; alkaline phosphatase, 333 U/L); positive screening antimitochondrial antibody (titre >1:640); positive SP100 autoantibodies; elevated IgM (18.21 g/L); and monoclonal protein of 14.0 g/L on serum protein electrophoresis with an IgM lambda peak on immunofixation. A biopsy of the left breast found (1) hyalinized collagen in the papillary, mid, and reticular dermis, (2) a lymphoplasmacytic perivascular inflammatory infiltrate with an absence of eosinophils, and (3) a lack of dermal mucin (Fig 2). Abdomen/pelvis magnetic resonance imaging (MRI) found a sclerotic process consistent with morphea profunda in the subcutaneous tissues of the abdomen and left thigh and within the paraspinal musculature (Fig 3, *A* and *B*).

FibroScan exhibited F1 liver fibrosis (5.3 kPa). The hepatology department confirmed the diagnosis of PBC and prescribed ursodiol, 1.5 g daily. Bone marrow biopsy findings were consistent with WM (25% to 30% atypical lymphoid infiltrate of marrow cells, lambda light-chain restricted CD19$^+$/CD20$^+$/CD22$^+$ B lymphocytes lacking CD5 and CD10).

For treatment of her WM, the patient received an induction protocol consisting of 6 monthly cycles of rituximab, 375 mg/m^2, and bendamustine, 180 mg/m^2. Improved skin tightness and induration were noted within 2 months of starting chemotherapy, with near

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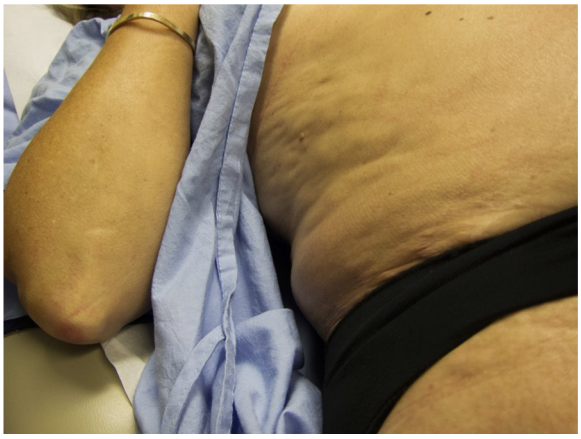

Fig 1. Flesh-colored, indurated plaques on the right flank.

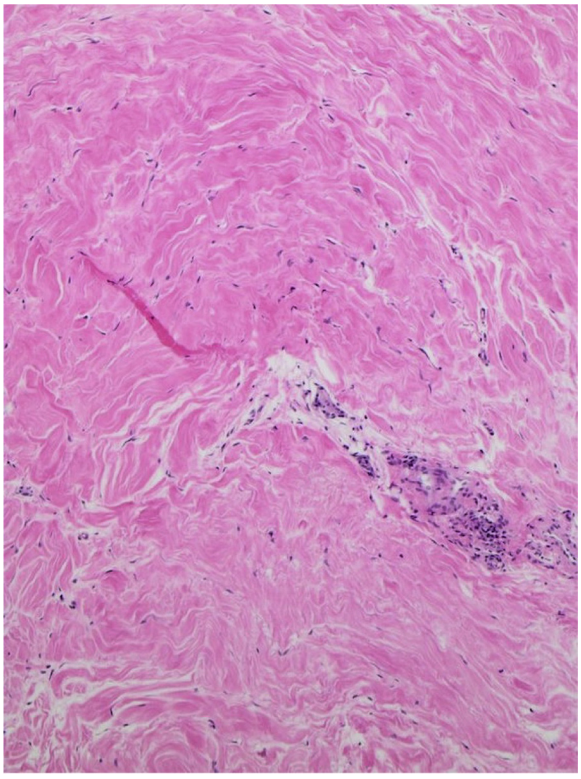

Fig 2. Punch biopsy of the left breast shows hyalinized collagen and a lymphoplasmacytic perivascular inflammatory infiltrate in the mid to reticular dermis. Colloidal iron stain failed to show an increase in dermal mucin. (Original magnification, ×10.)

complete clearance of her morphea after 6 treatment cycles. Two months after stopping treatment, the patient experienced a flare of her morphea in the abdominal region. Administration of rituximab alone provided relief of her skin symptoms. As she repeatedly experienced flares of her morphea 2 months after receiving rituximab, maintenance monotherapy with

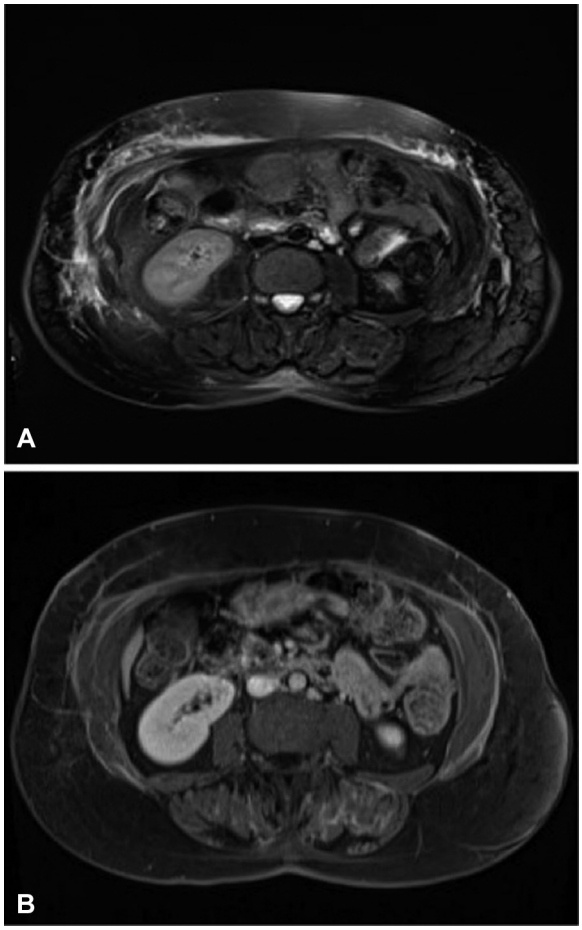

Fig 3. A, MRI shows increased T2 signal in the deep subcutaneous tissues of the abdomen, consistent with morphea. **B**, MRI T1 fat saturated after gadolinium shows linear enhancement in the paraspinal musculature.

rituximab (375 mg/m^2 every 3 months) is required to control her skin disease.

DISCUSSION

Approximately 18% of patients with morphea have a concomitant autoimmune disorder.[4] Although the association between limited systemic sclerosis and PBC is well established, the link between morphea and PBC remains less clear. Ten cases of morphea have been described in association with PBC (Table I).[5-13] Early intervention of asymptomatic patients with ursodeoxycholic acid may delay histologic progression of PBC.[14] Abnormal liver enzymes in a patient with morphea should therefore prompt assessment for autoimmune-mediated liver disease.

Disorders of skin fibrosis have been reported in 20 patients with plasma cell dyscrasias (Table II),[15-21] with only 1 case report documenting a relationship between morphea and WM.[3] In patients with monoclonal gammopathies, findings suggest that a

Table I. Morphea associated with primary biliary cirrhosis in the literature

Case	Author/year of publication	Sex/age of patient	Morphea variant	Antimitochondrial antibody titre
1	Resorlu, 2017[5]	F/56	Generalized	Positive, no titre reported
2	Iga et al, 2015[6]	F/68	Generalized	Strongly positive AMA-M2, no titre reported
3	Gonzalez-Lopez et al, 2006[7]	M/62	Generalized	AMA-M2 > 1:320
4	Reed et al, 2000[8]	M/34	Generalized	AMA-M2 positive, no titre reported
5	Goring et al, 1998[9]	F/>50	Generalized	1:1280
6	Goring et al, 1998[9]	F/>50	Generalized	1:40
7	Fujimoto et al, 1996[10]	NS/NS	Generalized	AMA positive, no titre reported
8	Wong and Holt, 1992[11]	F/54	Generalized	1:1600
9	Suyama, 1986[12]	F/50	Generalized	NS
10	Natarajan and Green, 1985[13]	F/58	Generalized	1:800

NS, Not specified.

Table II. Morphea associated with plasma cell dyscrasias in the literature

Case	Author/year of publication	Sex/age of patient	Diagnosis	Plasma cell dyscrasia
1	Magro et al, 2013[3]	F/61	Morphea	WM
2	Magro et al, 2013[3]	F/68	EF	MM
3	Magro et al, 2013[3]	M/61	Morphea	MGUS
4	Magro et al, 2013[3]	F/60	SS	MM
5	Magro et al, 2013[3]	F/70	Morphea	POEMS/MZL lung
6	Magro et al, 2013[3]	F/77	SS	MGUS
7	Magro et al, 2013[3]	F/83	EF	MGUS
8	Magro et al, 2013[3]	F/61	EF	MGUS
9	Magro et al, 2013[3]	F/63	EF	MGUS
10	Magro et al, 2013[3]	M/85	EF/SS	MM
11	Reyes et al, 2008[15]	F/31	SS	MM
12	Paredes-Suarez et al, 2005[16]	M/69	SS	MGUS
13	Bachleitner-Hoffman et al, 2002[17]	F/73	EF progressing to SS	MGUS
14	Nakanishi et al, 1989[18]	M/50	EF	MM
15	Jablonska and Stachow, 1972[19]	M/45	Morphea	MM
16	Khanna et al, 2002[20]	F/48	EF	MM
17	Endo et al, 2016[21]	F/68	Morphea	MGUS
18	Endo et al, 2016[21]	F/58	Morphea	MGUS
19	Endo et al, 2016[21]	M/76	Morphea	MGUS
20	Endo et al, 2016[21]	M/38	Morphea	MGUS

EF, Eosinophilic fasciitis; *MGUS*, monoclonal gammopathy of undetermined significance; *MM*, multiple myeloma; *MZL*, marginal zone lymphoma; *POEMS*, polyneuropathy organomegaly endocrine dysfunction monoclonal gammopathy; *SS*, systemic scleroderma.

circulating plasma cell–derived factor induces fibroblast proliferation, matrix synthesis, and collagen deposition.[3] Neoplastic plasma cells may also bind to stromal cells, up-regulating transforming growth factor-β expression and promoting collagen production.[22]

The extent and severity of morphea are important factors in determining the most appropriate treatment regimen. Topical therapies, phototherapy, and systemic immunosuppressants are important therapeutic modalities.[23] For the treatment of WM, our patient received a combination of bendamustine and rituximab. Both bendamustine, an alkylating agent derived from nitrogen mustard, and rituximab, a chimeric monoclonal antibody against the B lymphocyte antigen CD20, may have contributed to our patient's initial response to treatment. However, ongoing rituximab monotherapy (375 mg/m^2) was successful in treating her morphea flares. Although 2 studies[24,25] document the efficacy of rituximab in the treatment of skin and lung fibrosis of systemic sclerosis patients, there is no evidence to support the use of bendamustine in sclerotic skin disease. Rituximab has also shown benefit for the treatment of cutaneous sclerosis associated with chronic graft-versus-host disease.[26] Whereas dysregulated donor B-cell responses may cause sclerosis in chronic graft-versus-host disease, there is no direct evidence to support a pathogenic

role for B cells in morphea.[26] Our patient's morphea is favored to represent a paraneoplastic process that improved with treatment of her underling malignancy. Maintenance rituximab therapy is required to prevent flares of her skin disease.

CONCLUSION

We describe a patient with a unique combination of morphea, PBC, and WM who responded to maintenance therapy with rituximab. Our report highlights that (1) plasma cell dyscrasias should be excluded in patients with generalized or pansclerotic morphea refractory to usual therapies, (2) abnormal liver enzymes in patients with morphea should prompt consideration of PBC, and (3) rituximab represents a novel therapeutic option for treatment-resistant or paraneoplastic disease.

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