Successful treatment of subcorneal pustular dermatosis targeting an underlying monoclonal IgA gammopathy

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INTRODUCTION

Subcorneal pustular dermatosis (SPD), or Sneddon-Wilkinson disease, is a rare neutrophilic condition recognized as a chronic and relapsing skin eruption that generally affects the trunk, particularly flexural sites. Albeit not pathognomonic, sterile subcorneal pustules filled with neutrophils and occasional eosinophils are often present as well as neutrophilic infiltration of the skin. Immunofluorescence is usually negative in contrast to the differential diagnosis IgA pemphigus.[1,2] A variety of disease associations, including IgA monoclonal gammopathy have been described.[1] Few data are available on clinical outcome of plasma cell targeted treatment of underlying IgA gammopathy in patients with SPD. In this case, we present a patient with clinical remission of SPD after treatment for plasma cell dyscrasia.

CASE REPORT

A 77-year-old male with underlying type 2 diabetes mellitus, hypertension, and previous *transient ischemic attack* presented with an 8-year history of symmetric distributed pustular rash affecting the axillae, groin, buttocks, lower abdomen, and proximal thighs (Fig 1). Skin biopsies demonstrated subcorneal neutrophilic collections with negative direct immunofluorescence, most consistent with SPD in several samples (Fig 2). Fungal stains were negative. Complete blood counts were normal as well as electrolytes, liver and kidney function. Protein electrophoresis of plasma was first performed 5 years after debut of skin rash and a monoclonal gammopathy of the IgA lambda type (approx. 1 g/L) was disclosed. Monoclonal gammopathy of uncertain significance was the conclusion following a hematological assessment. The monoclonal gammopathy did not increase during the following 2 years. Urine protein electrophoresis was not performed. Then a bone marrow biopsy and flow cytometric analysis of a bone marrow aspirate identified an IgA lambda restricted plasma cell population accounting for less than 1% of the bone marrow cellularity. Conventional chest radiography was normal.

Previously, the patient was nonresponsive to high potency topical steroids, dapsone, systemic tetracyclines, colchicine, and mycophenolic acid. He tried 6 months therapy with adalimumab as well as acitretin in combination with narrowband UV-B 3 times a week for 8 weeks. He experienced

Abbreviation used:

SPD: subcorneal pustular dermatosis

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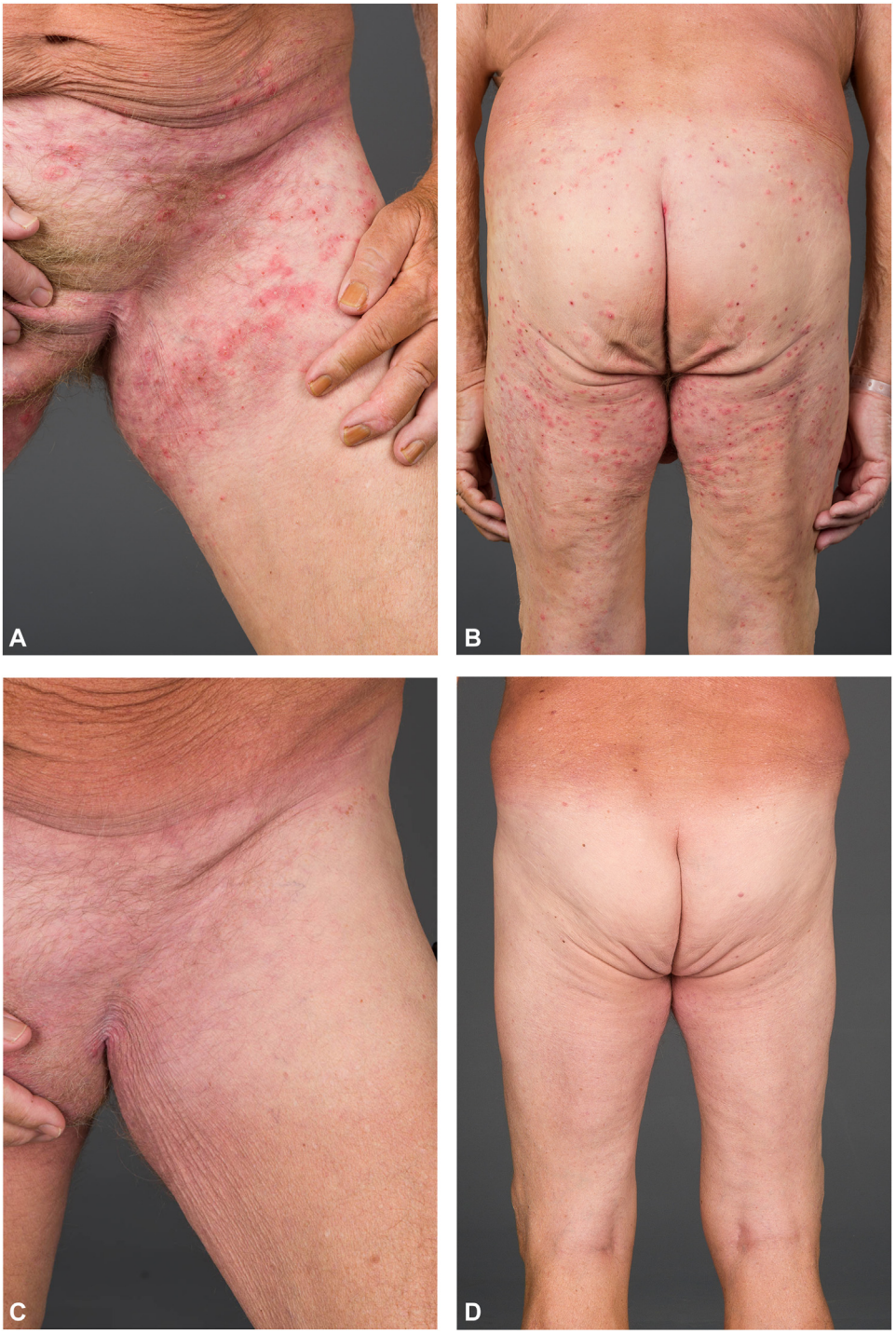

Fig 1. Multiple lesions at different stages of evolution including papules, pustules, and erythematous lesions with scaling and erosions located to the groin, buttocks, lower abdomen, and proximal thighs before treatment (**A** and **B**). Clinical remission after treatment (**C** and **D**).

transient improvement with repeated potassium permanganate baths and topical steroids when hospitalized with quick relapse after discontinuation. Systemic corticosteroids (prednisolone 0.5-1 mg/kg) gave a stabilizing effect but with the unwanted side effect of poorly controlled hyperglycemia and development of insulin-dependent diabetes mellitus type 2.

Considering the monoclonal IgA lambda as a putative underlying cause of the dermatosis, we suggested to the patient to start treatment for the plasma cell dyscrasia. He received treatment consisting of 4 cycles, and each cycle lasted for 21 days with no treatment delivered between day 17 and 21 (Table I). The treatment was well tolerated with no adverse events except for injection site hematomas. By the end of treatment his dermatosis had resolved (Fig 1), and complete hematological remission was achieved as assessed by flow cytometry of a bone marrow aspirate and plasma protein electrophoresis (Table II). He remains free of symptoms 12 months after completed therapy, and biannual dermatological and hematological assessment, including protein electrophoresis of plasma, complete blood counts as well as liver and kidney function are planned indefinitely.

DISCUSSION

The first-line management of SPD is oral dapsone.[2,3] Second-line therapies such as phototherapy (psoralen plus UV-A, broadband or narrowband UV-B), acitretin, and high potency topical or oral glucocorticoids are effective in some cases.[2,3] Some patients improve with topical tacalcitol, sulfapyridine and sulfamethoxypyridazine, colchicine, cyclosporine, mycophenolate, and biologic agents such as tumor necrosis factor inhibitors or interleukin 23 inhibitors.[2,3] Other reports suggest that doxycycline, trimethoprim-sulfamethoxazole, ketoconazole, and azithromycin might improve SPD.[2,3]

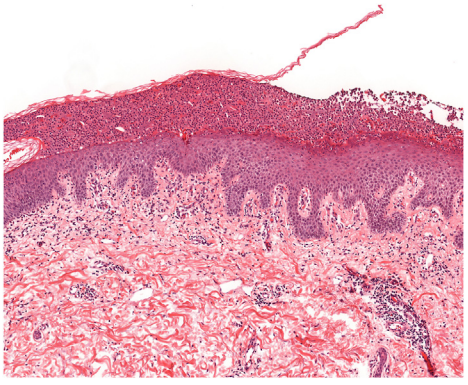

Fig 2. Histology. Subcorneal pustule with neutrophils. In epidermis under the pustule, there is spongiosis and exocytosis of neutrophils.

Many of the conventional SPD treatments were proven ineffective in our patient. Although mostly occurring as a separate skin disease, SPD is associated with other neutrophil-mediated dermatoses such as pyoderma gangrenosum and Sweet syndrome, leading to the hypothesis of a continuous spectrum of neutrophilic diseases.[4] Associated diseases include a number of autoimmune disorders as well as hematologic disorders such as paraproteinemias, predominantly IgA monoclonal gammopathy.[1] The pathophysiology is unknown, but findings have suggested 2 main mechanisms as either a polyclonal hereditary activation of the innate immune system or a clonal somatic activation of myeloid cells.[5] The presence of monoclonal gammopathy of IgA lambda in our patient, despite lack of IgA in skin biopsy, indicated a causal relationship between the monoclonal IgA and SPD.

Previous reports suggest that treatment of an associated underlying disease may improve the SPD. To our knowledge, there are limited case reports published on the treatment of subclinical plasma cell disease in patients with SPD. One previous report mentions treatment of a patient with SPD and a concurrent monoclonal IgA gammopathy, which transformed to multiple myeloma. The patient received intensive plasma cell directed treatment (high-dose melphalan and autologous stem cell transplantation) when multiple myeloma was ascertained and experienced complete remission of multiple myeloma as well as a sustained remission of SPD. Less than a year later the monoclonal gammopathy reappeared and subsequently also the SPD. This suggested a causal relationship between the monoclonal gammopathy (monoclonal gammopathy of clinical significance) and the dermatosis.[6] Another case reported a patient with IgA multiple myeloma associated SPD type of IgA pemphigus, who experienced long-term remission of the skin and hematological condition after treatment with a bortezomib-based regimen and subsequent

Table I. Treatment for plasma cell dyscrasia

	Day 1	Day 2	Day 8	Day 9	Day 15	Day 16
Bortezomib subcutaneous	1.3 mg/m^2		1.3 mg/m^2		1.3 mg/m^2	
Lenalidomide peroral	25 mg daily day 1-day 15					
Dexamethasone peroral	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg

Table II. Laboratory data

	Start of treatment	Response evaluation	Reference value
Hemoglobin g/dL	15.8	14.5	13.4-17.0
Thrombocytes $\times 10^9$/L	311	308	145-390
Leukocytes $\times 10^9$/L	8.1	5.6	3.5-10.0
Granulocytes $\times 10^9$/L	5.3	3.1	1.5-7.3
Lymphocytes $\times 10^9$/L	1.9	1.5	1.1-3.3
Monocytes $\times 10^9$/L	0.7	0.8	0.2-0.8
Creatinine umol/L	72	84	60-105
IgG g/L	7.4	7.6	6.1-14.9
IgA g/L	4.9	2.2	0.7-4.3
IgM g/L	0.38	1.1	0.4-2.1
Ig kappa mg/L	15.2	21.3	4.0-25.0
Ig lambda mg/L	18.3	14.4	6.0-27.0
Monoclonal IgA lambda g/L	1	Not detected	0

Ig, Immunoglobulin.

lenalidomide-based regimen when the disease relapsed.[7]

In this case, the patient received treatment for the underlying plasma cell dyscrasia, which resulted in complete regression of SPD in parallel with sustained hematological remission for at least 12 months. This indicates causality between SPD and associated monoclonal gammopathy, and treatment targeting the underlying plasma cell dyscrasia should be considered for patients with therapy resistant SPD and a monoclonal gammopathy.

Medical photography and illustration service, University of Oslo.

Conflicts of interest

None disclosed.

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