

Granulomatous Pigmented Purpuric Dermatitis Associated with Primary Sjögren's Syndrome

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Granulomatous variants of pigmented purpuric dermatoses (GPPD) were first described in 1996 (1). These reports suggested significant relationships between GPPD and autoimmune disorders (2–4). In addition, Kaplan et al. (2) recently reported the immunological profiles of GPPD and described the infiltration of significant numbers of CD4+ cells in granulomatous tissues, suggesting that, like sarcoidosis, immunological mechanisms might be associated with the formation of granuloma.

Sjögren's syndrome (SS) is an autoimmune disorder characterized by dry eyes and dry mouth due to lymphocytic infiltrates in the lacrimal and salivary glands. The various cutaneous manifestations of SS include dry skin, immunological inflammatory conditions such as vasculitis, and hypergammaglobulinemic purpura (4). Among them, in rare cases, SS is associated with granulomatous disorders, such as sarcoidosis (5). We describe here a case of GPPD associated with SS and demonstrate immunohistochemical staining for granuloma-forming cells, focusing especially on Foxp3+ regulatory T cells.

CASE REPORT

A 68-year-old Japanese woman visited our outpatient clinic with a 10-year history of pruritic, pigmented macules on her lower legs. She had been diagnosed with SS 10 years before and, at the same time, she noticed pigmented macules on her lower legs. On her initial visit, physical examination revealed brownish, leaf-like macules in patches on her lower legs (Fig. 1). A biopsy specimen revealed superficial granulomatous dermatitis with lymphocytes palisaded around a dense histiocytic core (Fig. 2A). Extravasated red blood cells were prominent in the upper dermis (Fig. 2B). Iron staining revealed a large amount of hemosiderin deposition in the upper reticular dermis (Fig. 2C). Immunohistochemical staining for Foxp3, as described previously (8), revealed a significant number of CD3+Foxp3+ cells throughout the granuloma (Fig. 2D). A full blood count and biochemical profile revealed increased levels of antinuclear antibody (ANA) ($\times 1,280$ (normal < 40)), anti-SS-A/Ro antibodies (138 U/ml (< 10 U/ml)) and anti-SS-B/La antibodies (138 U/ml (< 15 U/ml)). The patient reported having dry eyes, and the results of a Schirmer's test were 4 mm for the left eye and 3 mm for the right eye, suggesting that she had keratoconjunctivitis sicca. From the above findings, the patient was diagnosed with granulomatous pigmented purpuric dermatitis accompanied by SS. She was treated with topical application of 0.1% diflucortolone valerate ointment twice a day for one month, but with no sign of improvement.

DISCUSSION

GPPD is a rare variant of pigmented purpuric dermatoses. To our knowledge, it has been described in only 14



Fig. 1. Brownish, leaf-like macules in patches on the lower legs.

patients in the English literature (1–3). In addition, it was reported that approximately 29% of patients (4/14) showed serological evidence of autoimmune dysregulation, including positive ANA and rheumatoid factor tests (2, 3). However, there is no report describing a GPPD associated with apparent systemic autoimmune disease. In this report, we describe a case of GPPD associated with SS.

In SS, various cutaneous manifestations have been previously reported. Cutaneous manifestations of SS include dry skin, immunological inflammatory conditions, such as vasculitis, hypergammaglobulinaemic purpura, and other associated conditions (4). In rare cases, SS is associated with granulomatous disorders, such as sarcoidosis, granuloma annulare, and granulomatous panniculitis (5–7). These reports suggested that the formation of granuloma in SS might be associated with systemic autoimmunity. Thus, in this report, we employed immunohistochemical staining for Foxp3, which is a well-known marker for regulatory T cells (Tregs).

Immunological tolerance to self-antigens is essential for the prevention of autologous reactions and autoimmune

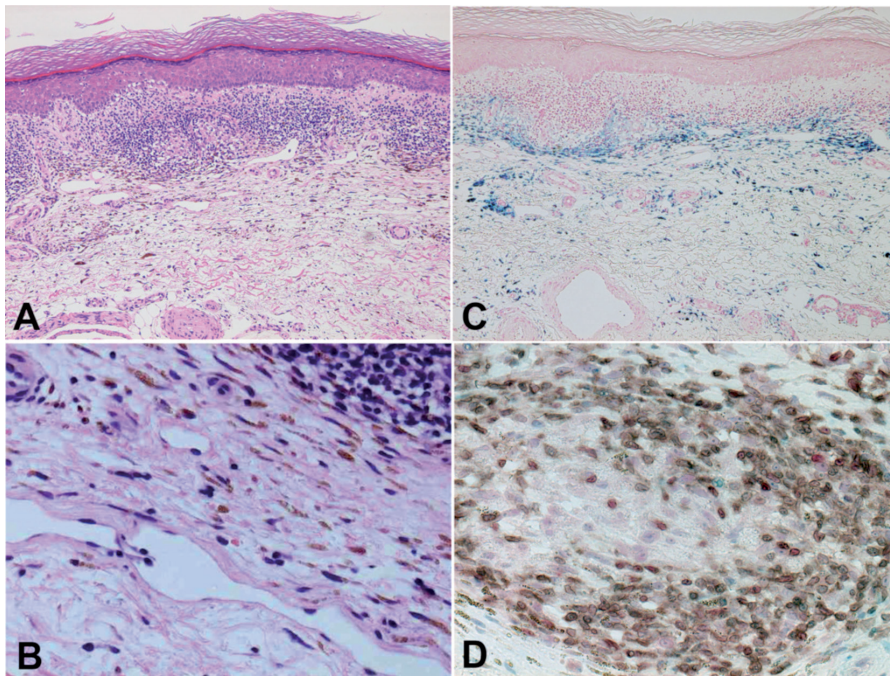


Fig. 2. (A) Superficial granulomatous dermatitis with lymphocytes palisaded around a dense histiocytic core (A, B). Iron staining revealed a large amount of hemosiderin deposition in the upper reticular dermis (C). A significant number of CD3+Foxp3+ cells were detected throughout the granuloma. A significant number of CD3+Foxp3+ cells were detected throughout the granuloma (D). Red: Foxp3, Brown: CD3. (A, C: $\times 100$, B, D: $\times 400$, original magnification).

diseases. In the peripheral organs, tolerance is reinforced by a variety of mechanisms, including a population of Tregs that actively suppress the function of autoreactive T cells. Foxp3, a member of the forkhead family transcription factor, is both necessary and sufficient for their development and function (9). Tregs are currently being examined for their roles in the pathogenesis of human diseases. In granulomatous tissue, Miyara et al. (10) reported the presence of Foxp3+ Tregs both in peripheral sarcoidosis granulomas and the peripheral blood of patients with sarcoidosis. Thus, sarcoidosis is associated with a global Treg cell subset amplification whose activity is insufficient to control local inflammation.

Concerning Foxp3+ Tregs in SS, several reports suggested that the numbers of Foxp3+ Tregs are positively correlated with SS (11, 12). Sarigui et al. (11) reported that Foxp3+ Tregs were enriched in the salivary glands and associated with the Chisholm score in primary SS. Moreover, Christodoulou et al. (12) reported that minor salivary gland-infiltrating Foxp3+ Tregs were positively correlated with the biopsy focus score, and a lower Foxp3+ cell incidence was correlated with adverse predictors for lymphoma development. These reports clearly suggested that the Foxp3+ Tregs frequency in the salivary glands of SS patients correlate with the prognosis of SS, and even suggested that Foxp3+ Tregs might be associated with pathogenesis of SS.

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