Possible involvement of SDF-1/CXCL12 in the pathogenesis of Degos disease

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Background: Degos disease or malignant atrophic papulosis is a rare occlusive vasculopathic disease characterized by pathognomonic cutaneous lesions and frequently fatal systemic involvement. The etiology of malignant atrophic papulosis remains unclear, and there is currently no effective treatment for malignant atrophic papulosis. Several chemokines can potentiate and expand the platelet response to increase thrombus formation. Among these chemokines, this study examined the expression of stromal cell–derived factor (SDF)-1/CXCL12, which is secreted by bone-marrow stromal and endothelial cells, activates megakaryocyte precursors, and costimulates platelet activation.

Objective: We sought to investigate and compare the expression of SDF-1/CXCL12 in tissue sections taken from 2 patients with Degos disease, 2 patients with other vaso-occlusive diseases, and 2 healthy control subjects.

Methods: Immunohistochemical staining involving antibodies to SDF-1/CXCL12 was performed on 3 skin biopsy specimens taken from 2 patients with Degos disease, 1 from a patient with antiphospholipid syndrome, 1 from a patient with cryoglobulinemia, and 2 from healthy control subjects.

Results: Strong SDF-1/CXCL12 staining was observed in the infiltrating inflammatory cells in the perivascular, intravascular, and perineural areas in tissue samples from patients with Degos disease. No staining was observed in samples from patients with antiphospholipid syndrome or cryoglobulinemia or from healthy control subjects.

Limitations: The number of cases available for evaluation was small. The findings were based primarily on the immunohistochemical results and were not confirmed using other techniques.

Conclusions: The intense staining of SDF-1/CXCL12 in lesions attributed to Degos disease, demonstrated for the first time to our knowledge in this study, suggests SDF-1/CXCL12 involvement in the pathogenesis of the disease. (J Am Acad Dermatol 2013;68:138-43.)

Key words: chemokine; CXCL12; Degos disease; malignant atrophic papulosis; stromal cell–derived factor-1; thrombosis.

Degos disease or malignant atrophic papulosis is a rare occlusive vasculopathic disease characterized by pathognomonic cutaneous lesions and frequently fatal systemic involvement. The etiology of Degos disease has not yet

Abbreviations used:

APS: antiphospholipid syndrome
EC: endothelial cell
SDF: stromal cell–derived factor

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Conflicts of interest: None declared.

Case 2 has been described in a case report (Demitsu T, Kakurai M, Murata S, Kiyosawa T, Yaoita H. Degos' disease associated with rheumatoid arthritis. J Dermatol 1997;24:488-90).

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been elucidated; however, several chemokines can activate the platelet response to increase thrombus formation.[1] Our treatment of 2 patients with Degos disease prompted us to investigate the immunohistochemical expression of 3 chemokines—stromal cell—derived factor (SDF)-1/CXCL12, monocyte-derived chemokine/CCL22, and thymus and activation-regulated chemokine/CCL17—which can activate platelet function.[1] Because endothelial cells (ECs) express SDF-1/CXCL12 but do not express thymus and activation-regulated chemokine/CCL17 or monocyte-derived chemokine/CCL22, we focused on the examination of SDF-1/CXCL12, a chemokine that interacts with CXCR4 receptors on platelets. Some previous studies have shown the role of SDF-1/CXCL12 in thrombogenesis in systemic lupus erythematosus, antiphospholipid syndrome (APS), or both. SDF-1/CXCL12 is a chemokine secreted by bone-marrow stromal cells and ECs, which activates megakaryocyte precursors and costimulates platelet activation.[2,3] We hypothesized that a thrombogenic phenomenon similar to that seen in cases of Degos disease also occurs in cases of other vaso-occlusive diseases. Therefore, we also examined skin samples taken from patients with APS and cryoglobulinemia and, for comparison with diseased samples, samples taken from healthy control subjects.

CAPSULE SUMMARY

- Degos disease is a fatal disease with an origin that remains unknown, although evidence suggests the involvement of a vaso-occlusive process.
- Stromal cell—derived factor-1/CXCL12, a chemokine that activates platelets, was densely stained in the lymphocytes around and inside the vessels of tissues obtained from patient with Degos disease.
- The presence of stromal cell—derived factor-1/CXCL12 in these tissues suggests that it plays a role in the pathogenesis of Degos disease.

CASE REPORT

Case 1

A 64-year-old Japanese woman was referred to our hospital for acute abdominal pain. She had a 2-year history of asymptomatic eruptions on her trunk and extremities and a history of recurrent acute abdominal pain of unknown origin. Her family history, medical history, and current medication regimen were unremarkable. Initial examination revealed the presence of reddish papules with crust, with occasional central atrophy on her trunk and extremities. Double-balloon enteroscopy and colonoscopy revealed edematous and erythematous mucosa with multiple erosions, ulcers, and scar formation of the small intestine and rectum—all of which were suggestive of ischemic enteritis. Microscopic examination revealed inflammation of the mucosa with dense lymphocytes; plasma cells; and eosinophil infiltration with ischemic change and erosion.

We noticed multiple reddish papules with central atrophy, with or without crusting. Close examination revealed telangiectasis surrounding a central porcelain-white atrophic lesion. Laboratory investigation indicated a normal blood cell count, a prolonged prothrombin time of 14.7 seconds (normal, 10.4-12.2 seconds), an activated partial thromboplastin time of 37.5 seconds (normal, 23.1-36.3 seconds), an increased level of D-dimer and fibrin/fibrinogen degradation products, a high titer of serum IgG, a high level of inflammatory marker C-reactive protein of 2.42 mg/dL (normal, <0.06 mg/dL), a rapid erythrocyte sedimentation rate of 72 mm/h (normal, 0-10 mm/h), a high serum ferritin level of 593.3 ng/mL (normal, 3-59.4 ng/mL), and the absence of antinuclear antibodies and anticardiolipin antibodies in the blood cells. Histologic examination revealed wedge-shaped degeneration of dermal collagen and thrombotic vessels at the bottom of the lesion.

Based on clinical observation and the results of laboratory testing, Degos disease with bowel involvement was diagnosed. After initial heparin treatment, the patient was placed on a medication regimen of 300 mg/d of warfarin and 300 mg/d of dipyridamole to treat her ischemic enteritis. Despite treatment, she died 4 months later because of bowel perforation and severe peritonitis.

Case 2

A 53-year-old Japanese woman previously given the diagnosis of hypertension and rheumatoid arthritis presented with asymptomatic reddish papules scattered on her trunk and extremities of 18-month duration. Skin examination revealed numerous small reddish papules with porcelain-white central atrophy and telangiectatic borders scattered on the front of her chest, abdomen, and entire back (Fig 1, *A* and *B*). There were no signs and symptoms of gastrointestinal or cerebral involvement.

Laboratory investigation revealed mild leukocytopenia and elevated rheumatoid factor IgG; slightly elevated antinuclear antibody and serum