CASE REPORT

Interstitial Granulomatous Dermatitis in a Patient with Prostate Cancer

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Interstitial granulomatous dermatitis (IGD) is a rare dermatosis, histologically characterized by an interstitial granulomatous infiltrate. It is associated with inflammatory arthritis, various medications, and autoimmune conditions. It is also associated with malignancies such as breast, endometrial, lung, and esophageal cancers as well as hematologic malignancies such as lymphoma and myelodysplastic syndrome. Herein we describe a case of IGD associated with prostate cancer, which has not been reported in the literature. (*Ann Dermatol* 29(3) 337~340, 2017)

-Keywords-

Interstitial granulomatous dermatitis, Prostatic neoplasm

INTRODUCTION

Interstitial granulomatous dermatitis (IGD) is a rare entity. It was first recognized by Ackerman et al. in 1993¹. Its clinical features are diverse. The exact pathogenesis of IGD remains unknown. Histological feature of IGD is interstitial infiltrate of histiocytes in the reticular dermis. IGD is associated with various systemic conditions, such as arthritis, autoimmune disease, connective tissue disease,

and internal malignancy²⁻⁶. We describe a rare case of IGD associated with prostate cancer. To the best of our knowledge, this is the first case of IGD in association with prostate cancer reported in the literature.

CASE REPORT

An 86-year-old man presented with pruritic, multiple, irregularly shaped, and erythematous to brown patches on the back for 3 weeks (Fig. 1). He had no other systemic symptoms. He had a history of cerebral infarction, hypercholesterolemia, and prostate cancer. He was taking chemotherapy agents (bicalutamide and triptorelin acetate) for prostate cancer. He had taken anticoagulant and statin agents for several years. On laboratory test, complete blood cell count, comprehensive metabolic panel, and urinalysis were unremarkable. His antinuclear antibody titer was low at 1:40. His anti-DNA titer was negative. Rheumatoid factor and thyroid function levels were normal. Test for anti-Ro/SS-A, anti-La/SS-b, p-ANCA, c-ANCA, SmJO1, or Scl70 was also negative. We initially considered pemphigus foliaceus, granuloma annulare, and contact dermatitis as clinical differential diagnosis. A skin biopsy of the lesion revealed interstitial histiocytic infiltration in the upper and mid-reticular dermis with few eosinophils and neutrophils. Alcian blue stain at pH 2.5 revealed no mucin deposition in the interstitial infiltrate (Fig. 2). After a month of systemic corticosteroids (prednisone 10 mg/day), the skin lesions were markedly improved.

DISCUSSION

IGD is a rare dermatological entity. Clinically, it is characterized by erythematous to violaceous patches or plaques symmetrically located on the upper trunk and proximal limbs. Linear subcutaneous cords or bands known as the

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Fig. 1. (A) Multiple, irregularly-shaped, and erythematous to brown patches on the back. (B) Close-up view.

Fig. 2. Skin biopsy of the lesion revealing interstitial histiocytic infiltration throughout the dermis with few eosinophils and neutrophils (H&E; A: $\times 40$, B: $\times 200$). (C) Alcian blue at 2.5 pH revealed no mucin deposition in the interstitial infiltrate ($\times 200$).

“rope sign” was considered pathognomic initially^{2,4}. However, this finding has only been reported in less than 10% of cases. Other morphologic findings of IGD include small skin-colored papules and plaques, diffuse macular erythema, annular plaques, polycyclic indurated plaques, annular scaly plaques, subcutaneous nodules, large atrophic hyperpigmented plaques, and periungual and mucosal erythema. IGD is mostly asymptomatic. It may have slight burning and/or itching^{2,4}.

Histopathological findings of IGD is characterized by interstitial arrangement of CD 68+ epithelioid histiocytes scattered throughout the dermis in varying densities, frequently around the foci of degenerated collagen^{2,6}. Rarely, eosinophils and neutrophils can be found in IGD. Vasculitis is generally absent^{2,5}. It might be difficult to differentiate interstitial granuloma annulare (IGA) from IGD clinically and histologically. In IGA, there is prominent mucin deposition. In addition, the histiocyte infiltrate is focal. However, in IGD, the histiocyte infiltrate tends to be more diffuse with deeper dermis and mucin deposition is minimal or absent^{2,3}. In our patient, Alcian blue stain at pH 2.5 revealed no mucin deposition. It had more diffuse histiocyte infiltrate, consistent with IGD.

The pathogenesis of IGD is unclear. However, since almost all cases are associated with an underlying inflammatory condition, IGD has been considered as a non-specific sign of immune dysfunction^{2,5}. The most accepted theory is that immune complexes in dermal vessels lead to inflammation and damaged collagen, resulting in granulomatous infiltrate².

IGD usually occurs in association with an underlying systemic disease. Diseases reported in association with IGD include inflammatory arthritis, particularly rheumatoid arthritis, and connective tissue disease such as systemic lupus erythematosus, and hematologic disorders such as lymphoma and myelodysplastic syndrome^{2,6}. Other IGD associated diseases reported in the literature include autoimmune thyroiditis and autoimmune hepatitis, Churg-Strauss syndrome, Behcet's disease, pulmonary paracoccidioidomycosis, pulmonary silicosis, antiphospholipid antibody syndrome, and *Borrelia burgdorferi* infection^{2,4}.

Medication related etiology of IGD has also been reported. Interstitial granulomatous drug reaction (IGDR) was first described in 1998 by Magro et al.⁷. IGDR is most frequently associated with antihypertensives such as angiotensin-converting-enzyme inhibitors, calcium channel blockers, beta blockers, and diuretics in addition to lipid-lowering agent, anticonvulsants, antihistamines, and tumor necrosis factor (TNF)-alpha blockers^{2,5,7}. Based on our patient's medication history, he had been taking statin agents for several years. Classically, IGDR has a delayed

onset (months to years after initiation of the associated drugs)⁸. Histopathologic findings of IGDR are different from those of classic IGD by vacuolar degenerative changes, exocytosis of lymphocytes, and absence of neutrophils^{2,5,7}. The histopathological findings of our patient were more consistent with those of IGD. Moreover, IGDR can completely resolve with drug cessation⁹. In reported cases of IGDR, reintroduction of suspected drug causes reappearance of the lesions^{9,10}. However, in our case, despite continued intake of statin agents, the lesions were improved after one month of systemic corticosteroids, indicating that drug related etiology was unlikely in our case.

In our case, the patient's absence of systemic symptoms and nonspecific laboratory findings excluded inflammatory arthritis and connective tissue disease. After excluding drug related etiology as mentioned above, IGD might have occurred in association with neoplasm in our patient. Our patient had prostate cancer which was diagnosed five months ago. There have been few reports of IGD in association with solid organ malignancies. Schreckenberg et al.¹¹ have revealed a case of interstitial granulomatous dermatitis and arthritis (IGDA) disclosing lung cancer. Moyano Almagro et al.¹² have also reported a case of IGDA disclosing esophageal cancer. IGDA disclosing malignant neoplasm in both cases may suggest paraneoplastic phenomenon^{11,12}. Peroni et al.³ have reported three patients with IGD who had cancer (hypopharyngeal cancer, breast cancer, and endometrial cancer, respectively) without articular symptoms. For these cases, the onset of most neoplasms associated with IGD was in close proximity to the onset of skin lesions. Our patient had been diagnosed with prostate cancer five months ago. Before the diagnosis of prostate cancer, he had nocturia and painful urination, and the prostate-specific antigen (PSA) level was 19.99 ng/ml (normal range, 0~4 ng/ml). He had been given chemotherapy since its diagnosis. When the skin lesions appeared 4 months later, the patient still had urinary discomfort, and the PSA level was 2.2 ng/ml. The patient was given systemic steroids (prednisone 10 mg/day), in addition to chemotherapy. After one month, the skin lesions markedly improved. At the same time, the prostate cancer was also in complete remission state, with the absence of urinary symptoms and the decrease of PSA level to 0.03 ng/ml. As the skin lesions improved after the remission of prostate cancer, it could be possible that IGD is associated with prostate cancer in our patient. Previous cases of IGD in association with solid tumor have also shown flares and improvement of clinical signs in accordance to the tumor state^{3,11,12}. In the case of IGDA disclosing lung cancer, four weeks after surgical removal of the tumor, the clinical signs disappeared¹¹. In a case of IGD with hypophar-

yngeal SCC, after the administration of systemic steroids, chemotherapy, and radiotherapy, there was complete remission of the skin lesions³. In contrast, in the case of IGDA disclosing esophageal cancer, due to tumor progression, the cutaneous lesions failed to improve despite systemic steroids, radiotherapy, and chemotherapy¹².

Treatment of IGD includes topical or systemic corticosteroids, dapsone, colchicine, methotrexate, and TNF- α blockers, and other immunosuppressants^{2,4,5}. Its prognosis is favorable with two-thirds of patients experiencing spontaneous remission after 3 months to 3 years²⁻⁶.

IGD is a rare distinct entity most frequently reported in association with rheumatologic or other autoimmune diseases. There have been only few reports of IGD in patients with solid organ malignancies. IGD in patients with prostate cancer has not been reported in the literature. Herein, for the first time, we report a rare case of IGD associated with prostate cancer.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Ackerman AB. Histologic diagnosis of inflammatory skin diseases: interstitial granulomatous dermatitis with arthritis. In: Ackerman AB, Guo Y, Vitale P, editors. *Clues to diagnosis in dermatopathology*. 1st ed. Chicago: ASCP Press, 1993:309-312.
2. Rosenbach M, English JC 3rd. Reactive granulomatous

dermatitis: a review of palisaded neutrophilic and granulomatous dermatitis, interstitial granulomatous dermatitis, interstitial granulomatous drug reaction, and a proposed reclassification. *Dermatol Clin* 2015;33:373-387.

3. Peroni A, Colato C, Schena D, Gisondi P, Girolomoni G. Interstitial granulomatous dermatitis: a distinct entity with characteristic histological and clinical pattern. *Br J Dermatol* 2012;166:775-783.
4. Veronez IS, Dantas FL, Valente NY, Kakizaki P, Yasuda TH, Cunha Tdo A. Interstitial granulomatous dermatitis: rare cutaneous manifestation of rheumatoid arthritis. *An Bras Dermatol* 2015;90:391-393.
5. Coutinho I, Pereira N, Gouveia M, Cardoso JC, Tellechea O. Interstitial granulomatous dermatitis: a clinicopathological study. *Am J Dermatopathol* 2015;37:614-619.
6. Thompson L, Abner S, Malone J, Callen JP. Interstitial granulomatous dermatitis as the initial manifestation of myeloma. *JAMA Dermatol* 2015;151:1141-1142.
7. Magro CM, Crowson AN, Schapiro BL. The interstitial granulomatous drug reaction: a distinctive clinical and pathological entity. *J Cutan Pathol* 1998;25:72-78.
8. Georgesen C, McDonough P, Cruz P. Interstitial granulomatous dermatitis associated with gabapentin. *Dermatitis* 2014;25:374-375.
9. Laura A, Luca P, Luisa PA. Interstitial granulomatous drug reaction due to febuxostat. *Indian J Dermatol Venereol Leprol* 2014;80:182-184.
10. Hernández N, Peñate Y, Borrego L. Generalized erythematous-violaceous plaques in a patient with a history of dyslipidemia. Interstitial granulomatous drug reaction (IGDR). *Int J Dermatol* 2013;52:393-394.
11. Schreckenberg C, Asch PH, Sibilía J, Walter S, Lipsker D, Heid E, et al. Interstitial granulomatous dermatitis and paraneoplastic rheumatoid polyarthritis disclosing cancer of the lung. *Ann Dermatol Venereol* 1998;125:585-588.
12. Moyano Almagro B, López Navarro N, Contreras Steyls M, Gallego Dominguez E, Herrera Acosta E, Herrera Ceballos E. Interstitial granulomatous dermatitis and arthritis revealing oesophageal carcinoma. *Clin Exp Dermatol* 2013;38:501-503.