

Granuloma Annulare in a Zoster Scar of a Patient With Multiple Myeloma

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Granuloma annulare (GA) is a common benign inflammatory skin disorder with an unknown pathogenesis. Granuloma annulare occurring in prior sites of herpes zoster (HZ) infection is rarely reported; however, it is the most common granulomatous reaction described at these sites. We report a case of localized GA on scars of prior HZ infection in a patient with multiple myeloma who had received an autologous peripheral stem cell transplant (PSCT). This patient's GA was successfully treated with intralesional corticosteroid injections.

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Granuloma annulare (GA) is a common benign inflammatory skin disorder with an unknown pathogenesis. Associations with several diseases such as diabetes mellitus and lymphoproliferative malignancies have been well-established, yet the exact mechanism has not been determined.¹⁻³ It has been suggested that a cell-mediated immune response triggered by a local or systemic stimulus may be involved in the disorder.⁴⁻⁷

Localized GA has been reported to occur in sites affected by trauma, vaccinations,^{8,9} or insect bites; resolving lesions of varicella and verruca vulgaris; sun-damaged skin⁴; and skin following tuberculin tests.^{1,3,10,11} Some cases have been reported of occurrence on dermatomal areas previously affected by herpes zoster (HZ) infection.^{1,3,12-15} We report a case

of localized GA at the site of scars from prior HZ infection in a patient with multiple myeloma who had received an autologous peripheral stem cell transplant (PSCT).

Case Report

A 54-year-old woman presented to our clinic with persistent shingles on the left side of her back and abdomen. She had a 2-year history of multiple myeloma and received thalidomide, dexamethasone, palliative radiation to the thoracic spine, and high-dose melphalan chemotherapy followed by autologous PSCT. The lesions were pruritic and painful. Two months prior to presentation and 2 weeks prior to her PSCT, the patient developed a painful and pruritic eruption on the left side of her back and abdomen. She initially attributed the discomfort to a previously diagnosed pathologic rib fracture but was subsequently diagnosed with HZ and started on a 7-day course of valacyclovir. The lesions crusted over and healed in approximately 2 weeks; she then underwent autologous PSCT while on prophylactic doses of valacyclovir approximately 1 month prior to presentation.

At presentation the patient had grouped pink to violaceous papules in a dermatomal distribution along the left side of her back, flank, and abdomen (Figures 1A and 1B). There were no hemorrhagic crusts or vesicles, but the papules were slightly tender to palpation. At that time, her diagnosis was postherpetic neuralgia with hypertrophic scars from HZ. A skin punch biopsy was performed and the patient was started empirically on gabapentin with progressively increasing dosages up to 300 mg 3 times daily.

Skin biopsy demonstrated palisading granulomas in the upper dermis with a lymphocytic infiltrate (Figure 2). Several multinucleated giant cells were apparent. Acellular areas were present within the center of the granulomas and showed positive staining for mucin with colloidal iron and Alcian yellow-toluidine blue (Leung) stains. Acid-fast and periodic acid-Schiff stains were negative for organisms.

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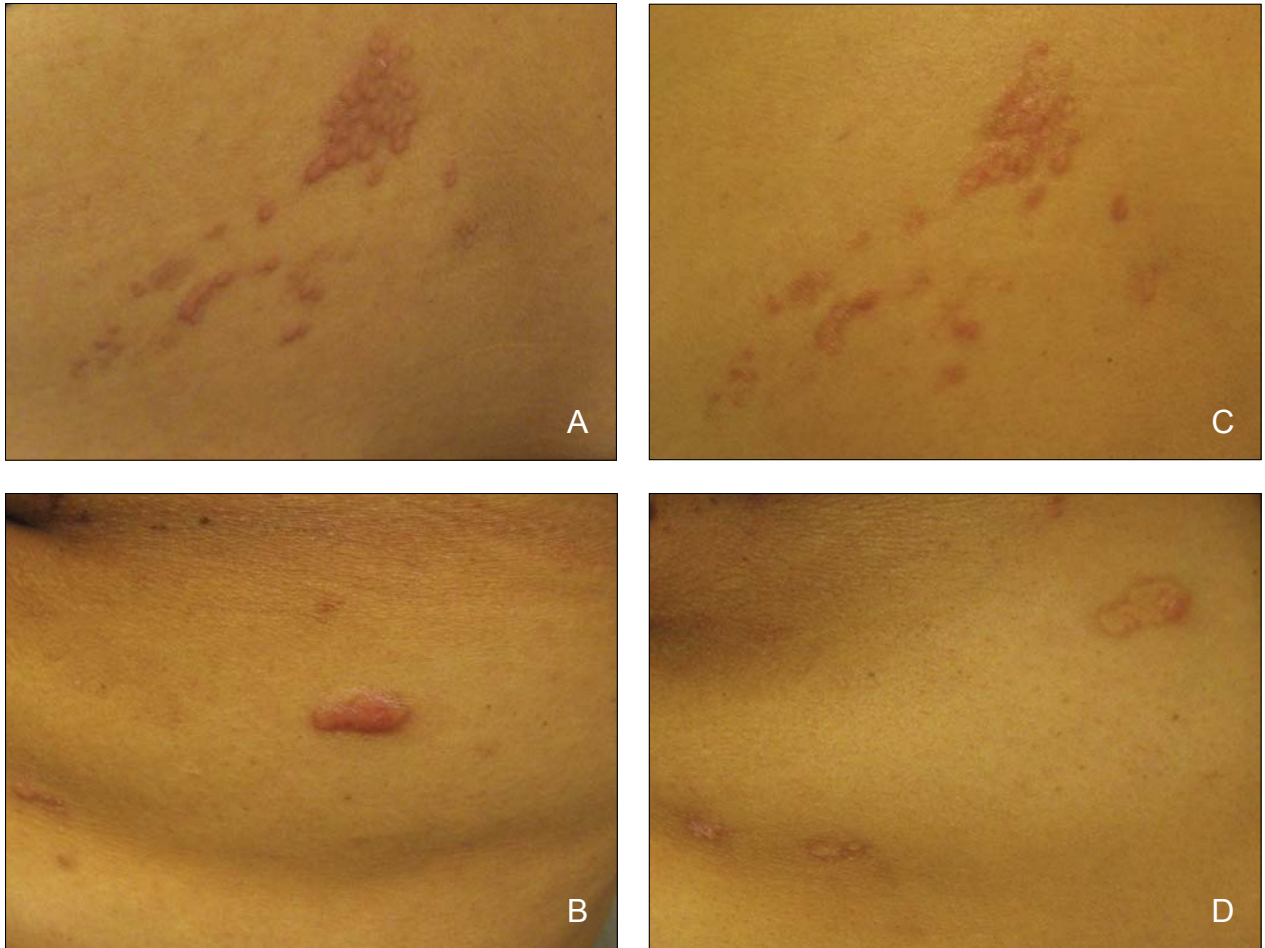


Figure 1. Grouped erythematous papules in a zosteriform distribution on the left side of the back (A) and an erythematous plaque on the left side of the abdomen (B). One month following intralesional triamcinolone acetonide injections, the patient demonstrated flattening of papules and decreased erythema on the back (C) and abdomen (D).

The patient was diagnosed with GA occurring in HZ scars. The gabapentin had not relieved her pain; as a result, she was given an intralesional triamcinolone acetonide injection at a concentration of 10 mg/mL. At 1-month follow-up she reported resolution of pain and pruritus at the locations of her prior eruptions. On physical examination her lesions demonstrated considerable flattening and decreased erythema (Figures 1C and 1D).

Comment

Etiology—Although GA occurring in prior sites of HZ infection is rarely reported, it is the most common granulomatous reaction described at these sites. Granulomatous reactions following HZ are rare and include GA, sarcoidosis, tuberculoid granulomas, granulomatous vasculitis, granulomatous panniculitis, and nonspecific granulomatous reactions.^{1-3,10,11,14-18}

Prior reports of GA after HZ infection show an equal sex distribution and an onset during the fourth or fifth decades of life.¹⁹ Granuloma annulare may develop at sites of resolved HZ with variable latency periods between the infection and the granulomatous reaction.² Based on reported cases, the interval between the eruption of HZ and the onset of GA is short, ranging from 1 week to 14 months.¹⁹ The lesions typically are papules that precisely trace the HZ scar. Histologic examination typically reveals foci of necrobiotic collagen surrounded by a palisade of histiocytes in the deep dermis and subcutis. Mucin deposits may be seen within the center of the palisaded granuloma with possible scattered multinucleated giant cells.¹⁹

Pathogenesis—Although the pathogenesis remains unclear, 3 different mechanisms have been proposed to explain the association of GA and HZ infection: an isotopic phenomenon, an immune complex

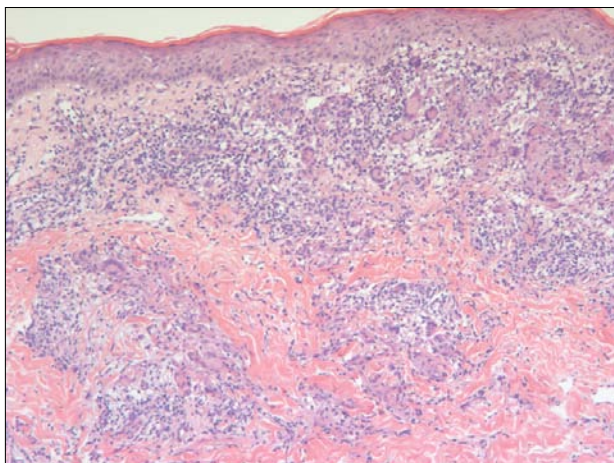


Figure 2. Superficial dermis with scattered granulomas and multinucleated giant cells (H&E, original magnification $\times 100$).

reaction, and an atypical delayed hypersensitivity reaction to HZ viral antigen.^{1,12,13,20} The term *isotopic response* was used to describe the occurrence of a new skin disorder at the site of another unrelated and already healed skin disease. It was thought that introducing the new term and classifying all the cases under a single keyword would make it possible to group occurrences of these phenomena together and simplify the search for an underlying mechanism.²¹ The pathogenesis stems from the fact that herpesviruses are known to specifically damage sensory nerve fibers,^{22,23} which leads to a dysregulation of the neuropeptides secreted from these fibers in the dermis. These changes locally affect several immune and angiogenic responses,^{20,24} which may result in a type of postherpetic neuroimmune dysregulation.²⁵ This imbalance may be responsible for the predilection and initiation of a localized isotopic response.²⁵

Circulating immune complexes have been found in the serum of patients with GA²⁶; immune complexes were detected in 4 of 5 patients with generalized disease and 5 of 10 patients with localized disease.²⁶ This finding supports the theory that the primary event in the pathogenesis of GA is formation of immune complexes and complement in the circulation and later deposition onto blood vessel walls.^{27,28} Complexes also may be locally formed by a reaction of an unknown tissue antigen, such as an antigen from HZ, with circulating antibody leading to an Arthus-like reaction.²⁸

The cell-mediated immune system's role has been supported by the presence of helper T cells and activated T lymphocytes in GA lesions occurring at sites of prior HZ infection.²⁹ Prior reports have documented the presence of varicella-zoster virus DNA

within early (<1 month) but not older postzoster GA lesions by using polymerase chain reaction analysis.^{2,30} The presence of varicella-zoster virus DNA in early lesions that histologically do not display viral cytopathic changes suggests the virus induces an atypical delayed hypersensitivity reaction not affected by antiviral therapy.² Another study using immunohistochemistry and in situ hybridization techniques to look at early granulomatous lesions concluded that major viral envelope glycoproteins (GpI and GpII) rather than complete viral particles could be responsible for delayed hypersensitivity reactions and could trigger granuloma formation following HZ infection.³¹

Localized GA also has been reported on HZ scars from prior infection 3 months after autologous PSCT in a man with Hodgkin disease.³² Many cases of GA occur after the diagnosis of a malignancy, suggesting that either the malignancy itself or immunosuppression caused by the cancer treatment is responsible for GA development.^{33,34} Generalized GA lesions in a patient with Hodgkin disease have been seen 3 weeks following autologous bone marrow transplant.³⁵ Because of the altered lymphocyte-mediated immune response during the immune system's early recovery period following transplantation,³⁶ a delayed hypersensitivity reaction to HZ antigens may lead to the development of GA in HZ scars. It has been suggested that granulomatous reactions on HZ scars are mainly due to atypical lymphocytic immune reactions to local antigenic stimuli.³²

Treatment—Localized GA, including GA associated with HZ infection, is generally self-limited and resolves within 1 to 2 years, whereas disseminated disease lasts longer.³⁷ No treatment other than reassurance may be necessary for localized GA, yet there are no well-designed randomized controlled trials of treatment options. Liquid nitrogen, injected steroids, or topical steroids under occlusion have been recommended for treatment of localized disease.³⁷ One study showed dramatically altered appearance of GA after application of imiquimod cream 5%.³⁸ Treatment of GA with the 595-nm pulsed dye laser was reported in a pediatric patient.³⁹ Disseminated GA has been treated with fractional photothermolysis using a 1440-nm Nd:YAG laser, with complete remission achieved after 2 to 3 treatment sessions.⁴⁰ Disseminated GA may be treated with one of several therapies such as dapsone, retinoids, niacinamide, antimalarials, psoralen plus UVA therapy, fumaric acid esters, tacrolimus, and pimecrolimus.³⁷

For GA associated with HZ infection, topical, intralesional, and systemic corticosteroids, as well as acyclovir, have been therapeutically used with inconsistent results. Although the pathogenesis

remains unclear, the theory that the virus induces an atypical delayed hypersensitivity reaction would refute the use of antiviral therapy.² Others have used a combined treatment with clobetasol propionate ointment 0.05% (twice daily) and oral pentoxifylline (600 mg twice daily); according to one report, all lesions cleared after 1 month.²⁵ Intralesional injections of triamcinolone acetonide have previously been used, causing flattening of the papules after 4 weeks of follow-up.¹⁹ Our patient was given intralesional triamcinolone acetonide injections with considerable flattening and decreased erythema at 1-month follow-up.

Conclusion

We report a case of a patient with multiple myeloma who developed GA in HZ scars after autologous PSCT. This patient responded well to intralesional triamcinolone acetonide injections. This case should serve to remind clinicians that eruptions in sites of healed HZ infection may represent a granulomatous reaction such as GA.

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