Included in the theme issue:
INFLAMMATORY SKIN DISEASES
Acta Derm Venereol 2012; 92: 339–409

Isotopic Response of Graft Versus Host Disease Following Herpes Zoster Infection: Case Report and Review of the Literature

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Accepted October 16, 2011.

Wolf's isotopic response is the occurrence of an unrelated cutaneous disorder in an area of healed skin previously affected by another pathology (1, 2), the most frequent being granulomatous reactions followed by dysimmune reactions and malignancies (3). Cutaneous graft versus host disease (GVHD) presenting as an isotopic response is very rare. We describe here an unusual manifestation of the aforementioned disorder and review the literature on this topic.

CASE REPORT

A 69-year-old Caucasian man presented with erythematous and hyperpigmented scaly plaques, which were either sharply or vaguely demarcated. They were predominantly located in the dermatome T4, with similar lesions on the upper back, shoulders and neck outside of T4 (Fig. 1).

His medical history revealed a myelodysplastic syndrome type refractory anaemia with excess blasts (RAEB), for which he had received an allogeneic stem cell transplant with a human leukocyte antigen (HLA) mismatch in December 2007 and donor lymphocytes in May 2008. He had received GVHD prophylaxis, comprising 30 mg methotrexate on day 1 after transplantation, and 20 mg on days 3 and 6, in addition to tacrolimus, starting a day before transplantation at 3 mg/day and reduced by 0.5 mg approximately every 3 weeks, over a period of 18 weeks. He had not developed an acute GVHD. He had received prednisolone for autoimmune hepatitis and polymyalgia rheumatica until one month before the appearance of his skin lesions, the maximum daily dose administered being 50 mg, which had been gradually reduced to 2 mg. The patient had had herpes zoster in the right dermatome T4 approximately 8 months before he presented at our department, which had been treated with ibuprofen 600 mg 3 times a day, tramadol 50 mg once daily and topically with fusidic acid gauze as an infection prophylaxis. As he had presented himself 10 days after the onset of symptoms, no aciclovir had been given. Due to persistent post-herpetic neuralgia, gabapentin 600 mg 3 times daily had been prescribed. He had been free of skin lesions for approximately 30 months after receiving allogeneic bone marrow transplantation (BMT).

Two 4-mm skin punch biopsies were taken, one from the upper back outside of T4 and another from the affected skin within T4.

Dermatohistopathological analysis revealed a superficial interface-dermatitis with hypergranulosis, orthohyperkeratosis and pigment incontinence, a complete loss of the epidermal stratum basale, as well as subepidermal detachment. A sparse and lymphocytic inflammatory infiltrate with a few eosinophilic granulocytes was present, but remained confined to the superficial dermis (Fig. 2). Dermatohistopathological differential diagnosis was a lichenoid drug eruption or a chronic GVHD. The sparse inflammatory infiltrate in the dermo-epidermal junction zone was unusual for a lichen planus or for a lichenoid drug reaction and the few eosinophils also did not strengthen the case for the latter diagnosis.

PCR did not detect varicella zoster virus (VZV)-DNA from a lesional skin sample. Serological testing with an enzyme-linked immunosorbent assay (ELISA) showed a borderline result for VZV IgM and a positive result for VZV IgG, compatible with a past VZV infection.

The patient was diagnosed with a post-herpetic isotopic response of GVHD following allogeneic stem cell transplantation, due to the consecution of skin lesions as well as dermatohistopathology. Topical therapy with triclosan 1% and betamethasone 0.2% in a petrolatum-based ointment was initiated and the patient was referred to private practice for further medical supervision.

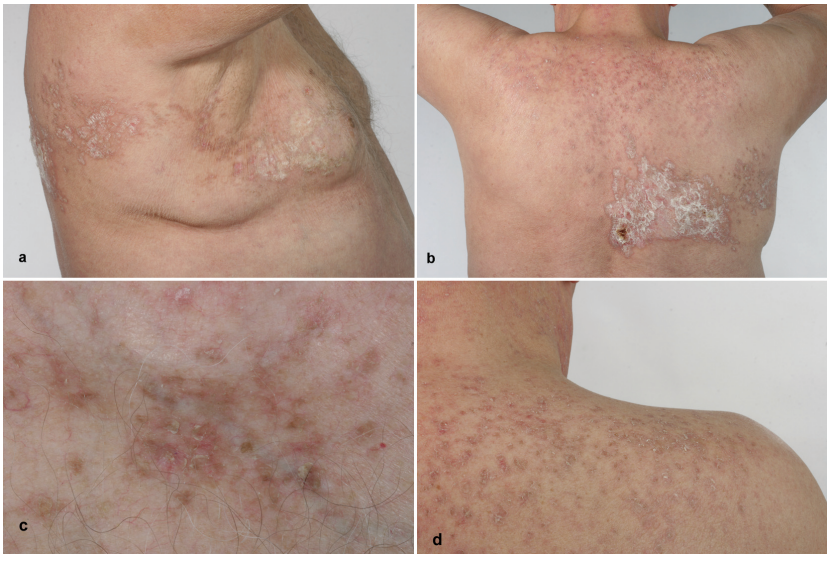

Fig. 1. Erythematous and hyperpigmented scaly plaques, either sharply or vaguely demarcated: (a) on the right side of the thorax, dermatome Th 4; (b) on the back, shoulders and neck; (c) on the chest, dermatome Th 4; and (d) on the upper back, outside of Th 4.

DISCUSSION

Infection with VZV or herpes simplex virus (HSV) is the most common predisposing skin disorder for an isotopic response (4).

Of all isotopic responses following a VZV/HSV infection, the secondary cutaneous pathology is, in most cases, a granulomatous reaction, with 60 cases recorded so far, followed by dysimmune reactions (45 cases), malignancies (32 cases), leukaemic or lymphomatous

 doi: 10.2340/00015555-1290
 ISSN 0001-5555

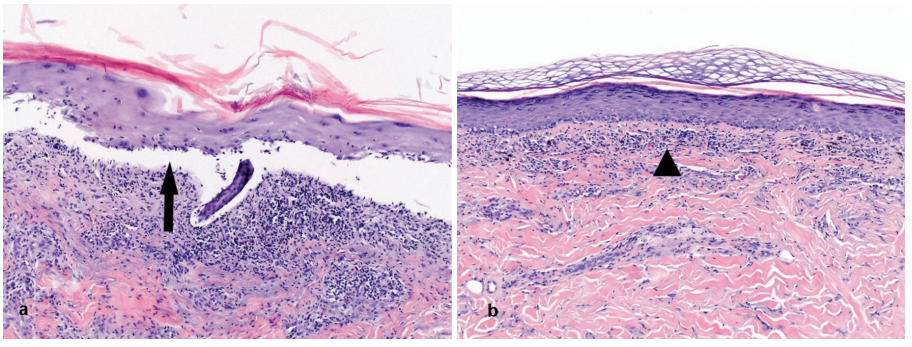

Fig. 2. Two skin biopsies taken from the upper back, (a) outside the area previously affected by herpes zoster and (b) from the area affected by herpes zoster. Superficial interface dermatitis with a lymphocytic infiltrate and pigment incontinence. In (a), complete loss of the stratum basale and décollement of the epidermis (*arrow*), hypergranulosis and orthohyperkeratosis. Infiltrate with eosinophilic granulocytes in the dermo-epidermal junction zone. In comparison, in (b), sparse lymphocytic infiltrate in the dermo-epidermal junction zone (*arrowhead*) with a vacuolar degeneration of the basement membrane. (a) Haematoxylin and eosin (H&E) ×200, (b) H&E ×100.

infiltrations (19 cases), infections (15 cases) or other various causes (23 cases), summarized in Table SI (available from: http: //www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1290) (3–7). The most common granulomatous reaction is granuloma annulare (3) and the prevailing immunoreactive lesions are lichenoid reactions (3). A wide range of malignancies can present as isotopic responses, ranging from skin metastasis of primary breast cancer (8), through squamous cell carcinoma (1) to leukaemic infiltration (9) or lymphoma (10). The dominance of fungal and viral infections hints at deficient local cellular immunity, as hypothesized by Ruocco et al. (3). A multitude of other skin pathologies can present as isotopic responses, including comedones (11), Stevens-Johnson syndrome (12) and keloid (13).

GVHD is a common complication of allogeneic BMT. It develops due to a HLA mismatch between the donor and the recipient, when mature donor T cells transplanted with the graft recognize the recipient's tissue as foreign and initiate an immunological response (14).

To date, seven cases of GVHD manifesting as a post-herpetic isotopic response have been described, as summarized in Table SII (available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1290) (15–19), as well as two cases following a dermatomal pattern, without a confirmed diagnosis of herpes zoster infection in the affected area (20). Three further linear GVHD reactions following Blaschko's lines (21–24) and one case of GVHD occurring in the area of total lymphoid irradiation (25) have been published. All patients with a post-herpetic GVHD had received allogeneic bone marrow transplantation. Our case brings the total of published cases of patients having developed GVHD as a post-herpetic isotopic response to eight. Nevertheless, this patient is the first recorded case of GVHD developing as a post-herpetic isotopic response presenting a dermatomal and non-dermatomal pattern.

The authors declare no conflicts of interest.

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