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SHORT COMMUNICATION

Non-infectious Panniculitis during Hydroxyurea Therapy in a Patient with Myeloproliferative Disease

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The cutaneous toxicity of the anti-tumour drug hydroxyurea (HU) has been well described. We report here a rare case of non-infectious panniculitis that occurred during HU therapy in a patient with myeloproliferative disease (MPD). Since no previous reports have described HU-associated panniculitis, it was difficult to diagnose this condition.

CASE REPORT

An 81-year-old woman was referred to our dermatology department with erythema on her knee that had appeared 3 days earlier. The patient reported having bruised her right knee a few weeks before and having developed the erythema after poultice application. Her medical history was significant for MPD at age 72 years, normal pressure hydrocephalus at age 77 years, and dissecting aortic aneurysm at age 79 years. She had been taking hydroxyurea, 500 mg daily, and acetylsalicylic acid, 100 mg daily, for 8 years as treatment for the MPD. Other medications included bisoprolol fumarate, candesartan cilexetil, amlodipine besilate, and lansoprazole. She had no recent episodes of infectious diseases. On examination, she was found to be afebrile and generally healthy. A 6-cm diameter, ill-defined erythema with mild swelling was seen on the left knee. No pain, tenderness or local heat was reported. Contact dermatitis or bacterial infection was suspected, and she was prescribed difluprednate ointment and cefdinir. One week later, the erythema expanded, developing mild localized heat, slight induration and mild exfoliation (Fig. 1). A punch biopsy from the erythema revealed infiltration of inflammatory cells, consisting of lymphocytes, plasma cells and eosinophils, in the mid- and deep dermis and subcutis. The subcutis showed septal panniculitis accompanying granuloma formation (Fig. 2). No evident aggregations of leukocytes were seen. No significant changes were seen in the epidermis, although mild orthohyperkeratosis was evident. Periodic acid–Schiff stain and Ziehl–Neelsen stain were negative for bacterial infection. Laboratory tests revealed a serum C-reactive protein level of 0.46 mg/dl (normal < 0.30 mg/dl), a leukocyte count of 23,600 cells/μl (normal 3,800–8,500 cells/μl), a platelet count of 1,060,000 cells/μl (normal 160,000–410,000 cells/μl) and a haemoglobin concentration of 16.7 g/dl (normal 11.0–16.0 g/dl) in the peripheral blood. Differential diagnoses included erythema nodosum, bacterial cellulitis, Wells syndrome and severe insect bite reaction. However, the history and the findings were not typical of any of these diseases, and definitive diagnosis could not be made. One month after the initial visit, the erythema further expanded to one-third of her left leg, but was neither ulcerated nor painful. She maintained a generally good condition. HU-associated skin toxicity or bacterial infection was suspected as the cause of the panniculitis, and prednisolone, 10 mg daily, in addition to minocycline hydrochloride, 100 mg daily, was started. Within one week of treatment, the erythema remarkably improved. Minocycline hydrochloride was discontinued, and the prednisolone was gradually tapered. Following remission of the eruption, the prednisolone was discontinued; however, this resulted in a prompt recurrence of the erythema. Treatment with prednisolone, 10 mg daily, was resumed. In addition, HU was discontinued and bimonthly ranimustine therapy was started. The erythema remitted rapidly and did not recur after subsequent tapering and discontinuation of the corticosteroid.

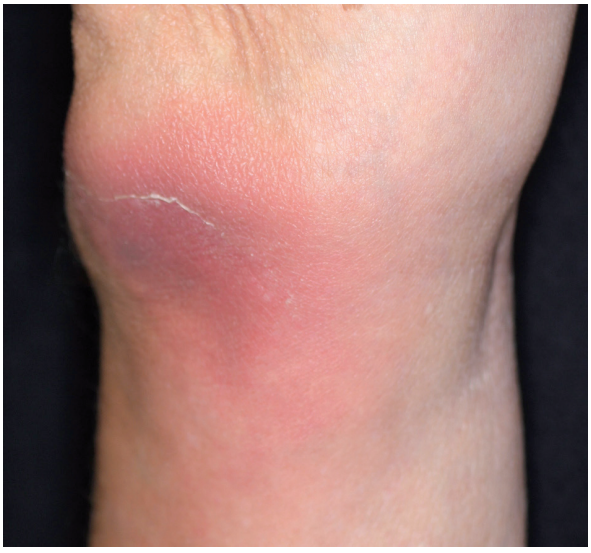

Fig. 1. Clinical features of the patient's eruption: an indurated erythematous nodule is visible on the right knee.

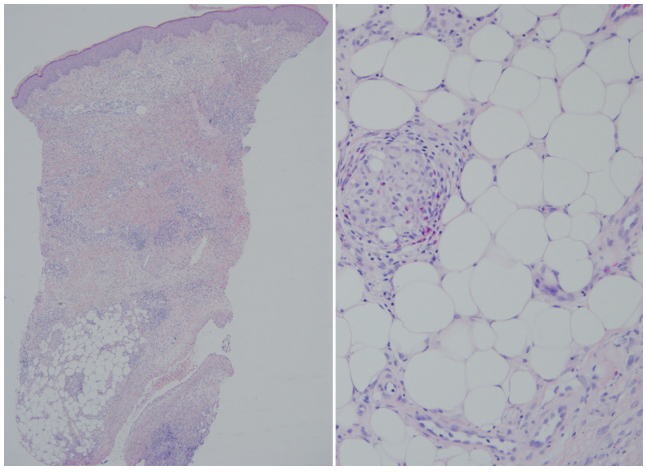

Fig. 2. Haematoxylin and eosin stained histological images of the skin biopsy. (a) The histopathological features show a deep dermal perivascular dermatitis with lymphocytes, eosinophils and plasma cells and a mixed panniculitis involving the septum and the lobule (original magnification ×40). (b) Focal granuloma formation is seen in the subcutaneous lesion (original magnification ×200).

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DISCUSSION

HU is an S-phase-specific inhibitor of *de novo* DNA synthesis that has been used as an anti-tumour agent since the 1960s (1). Today, it is widely used for the treatment of MPD, leukaemia and sickle cell anaemia. Although HU is a relatively well-tolerated drug, it has been associated with various cutaneous complications (1–3). One of the most severe cutaneous complications is HU-induced cutaneous ulcers, which appears in approximately 3–5% of MPD patients receiving HU therapy (2–4). The ulcers often appear as multiple, painful, retractable leg ulcers, often resulting in cessation of the HU treatment (3, 5, 6). Another characteristic complication is HU dermopathy (7), which presents as acral and facial erythema that sometimes resembles the cutaneous signs of dermatomyositis (7–10).

The histopathology of HU-induced ulcers shows non-specific features with occasional leukocytoclastic vasculitis or fibrinoid thrombi (5, 6, 9). HU dermopathy is characterized by focal lichenoid reaction accompanied by liquefaction degeneration of the basal layer (7–9). The pathogeneses of these conditions are unclear, but minor tissue damage may be triggers of the skin lesions, and a disturbed replicative capacity of basal keratinocytes due to HU may be a key factor (3, 7). Other suspected pathomechanisms include disturbed microcirculation caused by HU-induced macrocytosis, direct cytotoxicity of HU, and microthrombi related to platelet dysregulation (3, 7, 9, 11). Other HU-associated skin changes include partial alopecia, increased pigmentation, skin atrophy, and nail changes (8, 9).

We were unable to find any literature reporting HU skin toxicity presenting as panniculitis, which made management of the present case difficult.

In the present case, bacterial infection was unlikely because antibiotics were ineffective and remission was achieved without antibiotics. In addition, no signs of other allergic disease, vasculitis, or systemic granulomatous disease were seen throughout the disease course. While the skin eruption was suppressed by low-dose prednisolone, complete remission was achieved only after discontinuation of HU. The skin eruption was preceded by bruising, which can be speculated to have triggered the pathogenic event, similarly to the proposed pathogenesis of HU-induced cutaneous ulcers and dermatomyositis-like HU dermopathy. In the present patient, it might not have been trauma to the epidermis, but rather, injury to the deep tissues that triggered the disease. From these findings, we regard the present case of panniculitis as non-infectious, mixed lobular and septal panniculitis associated with HU therapy. However, we were unable to completely exclude other possibilities, such as the possibility that the MPD may have contributed to the pathogenesis, similar to HU dermopathy that generally affects patients with haematological neoplasms (3, 7).

In summary, we report here mixed lobular and septal panniculitis in a MPD patient, which was considered to be a previously undescribed complication of HU therapy. The panniculitis responded well to low-dose prednisolone, but cessation of HU was necessary for complete remission.

The authors declare no conflicts of interest.

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