CLINICAL REPORT

Papular Neutrophilic Dermatosis and Erythema Elevatum Diutinum Following Erythropoietin Therapy in a Patient with Myelodysplastic Syndrome

EMANUELA GUBINELLI, BARBARA COCUROCCIA, MARCELLO FAZIO, GIORGIO ANNESSI and GIAMPIERO GIROLOMONI
Istituto Dermopatico dell’Immacolata, IRCCS, Rome, Italy

A 65-year-old man with refractory anaemia with an excess of blasts developed an erythematous papular eruption symmetrically distributed on the legs and trunk 3 months after initiation of erythropoietin therapy. The lesions showed a dense neutrophilic infiltrate in the absence of leucocytoclastic vasculitis, and did not fit the criteria of a well-defined neutrophilic dermatosis. Concomitant with the rapid resolution of these skin lesions following erythropoietin discontinuation, typical lesions of erythema elevatum diutinum arose on the extensor surface of the fingers, knees and elbows, which responded to a brief course of dapsone treatment. Although typical and atypical neutrophilic dermatoses have been reported in patients with haematological disorders, they have also been associated with the use of drugs, in particular granulocyte colony-stimulating factor. To our knowledge this is the first report of unclassified neutrophilic dermatosis and erythema elevatum diutinum occurring following the administration of erythropoietin. Key words: erythema elevatum diutinum; erythropoietin; myelodysplastic syndrome; neutrophilic dermatosis.

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Giampiero Girolomoni, Istituto Dermopatico dell’Immacolata, IRCCS, Via Monti di Creta 104, I-00167 Rome, Italy. E-mail: giro@idi.it

Infiltration of the skin by neutrophils is a common feature of many skin diseases, including infectious, inflammatory and neoplastic disorders (1). Neutrophilic dermatoses (ND) comprise a spectrum of diseases characterized by heavy infiltration of the skin, with normal polymorphonuclear leucocytes in the absence of microorganisms. Moreover, ND are responsive to corticosteroids or other immunosuppressive agents. Typical ND include pyoderma gangrenosum, Sweet’s syndrome, subcorneal pustular dermatosis of Sneddon-Wilkinson, erythema elevatum diutinum (EED), granuloma faciale and neutrophilic eccrine hidradenitis (2). In addition, there are patients with clinico-pathological entities with overlapping features and reports of atypical ND that could not be categorized. These conditions can occur simultaneously or separately in the same patient, supporting the notion that ND represent a continuous spectrum of diseases encompassing well-defined entities (2–4). Further arguments linking the different ND are the frequent association with systemic diseases (e.g. haematological disorders, inflammatory bowel diseases and arthritis) and the possible occurrence of extra-cutaneous neutrophilic infiltrates in the lymph nodes, lung, bone, liver and spleen (5).

Recently, drugs have been implicated as causative agents in some cases of ND (6–10), with haematopoietic growth factors as the most commonly reported drugs (11–14). We describe here the case of a man with refractory anaemia with an excess of blasts (RAEB) who developed an undefined papular ND and then a typical EED after a few months of erythropoietin therapy.

CASE REPORT

A 65-year-old Caucasian man was seen in our Department in January 2002 with a 3-month history of an asymptomatic papular eruption involving the legs and trunk. The patient was diagnosed as having RAEB in January 2001, and in June 2001 started treatment with recombinant erythropoietin (10,000 UI 3 times/week) for severe anaemia unresponsive to transfusions. The patient was also taking low-dose prednisone (10 mg/day). No other drugs had been used prior to development of the skin lesions. Physical examination revealed numerous red-brownish papules symmetrically distributed on the trunk, thighs, legs and plants (Fig. 1a–c). A biopsy specimen showed a diffuse upper dermal infiltrate composed mainly of neutrophils with nuclear dust and histiocytes. Some extravasated erythrocytes were present along with endothelial cell swelling but no overt signs of vasculitis (Fig. 1d). Electron microscopy confirmed that the infiltrate was composed primarily of normal neutrophils and macrophages. Routine laboratory tests were within normal limits, with the exception of haemoglobin 7.9 g/dl (normal values 12–16 g/dl), haematocrit 23.7% (37–47%), platelets 71,000/µl (150–400/µl) and hypergammaglobulinaemia (2.27 g/dl; 0.7–1.7 g/dl). Rheumatoid factor and antinuclear antibodies...
were absent. The number of circulating T cells, B cells and natural killer cells was within the normal range. A bone marrow biopsy showed increased cellularity, dyserythropoietic changes and ringed sideroblasts in the erythroid lineage. Granulocytic series had morphological abnormalities with 10% blast cells and dysgranulopoiesis. Micromegakaryocytes with marked atypia and an increased percentage of lymphocytes, not exceeding 15–20%, were also present. X-ray of the chest and bones (skull, hands, lumbar spine and bones of the lower limbs), as well as abdominal echo-scan and total body CT scan, did not reveal abnormal findings, except splenomegaly. Cutaneous lesions flattened and turned into hyperpigmented macules 10 days after erythropoietin discontinuation with almost complete resolution after one month in the absence of active treatment. However, while papular lesions were fading new lesions appeared symmetrically on the extensor

Fig. 1. Symmetrically distributed erythematous-brownish monomorphic papules on the lower limbs (a–c). Histology showed a diffuse dermal infiltrate of neutrophils and histiocytes along with nuclear dust (d). Endothelial cell swelling and extravasated erythrocytes were present, but no signs of vasculitis could be detected (H&E, 160×).

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surface of the fingers of the hands, elbows and knees. These consisted of indurated violaceous nodules and plaques of variable size and configuration (Fig. 2). Histology of these lesions showed the typical features of EED with a dense dermal infiltrate of neutrophils, fibrinoid necrosis of small vessels, abundant nuclear dust and extravasated erythrocytes. As these lesions progressively worsen, dapsone therapy (100 mg/day) was started. Marked improvement and then complete resolution of the lesions was obtained after 4 and 8 weeks, respectively. Complete remission of all skin lesions was observed at a 4-month follow-up.

DISCUSSION

ND comprise a group of diseases which it is important to recognize because they are frequently associated with serious extracutaneous disorders. Although in many instances ND can be classified according to the initial description, there is an increasing number of reports of patients affected by ND with overlapping features, atypical ND or ND that do not fit the classical type ND (2–5). The overlap between bullous pyoderma gangrenosum and atypical Sweet’s syndrome was first emphasized by Caughman et al. (15), who suggest that both entities, when associated with myeloproliferative disorders, form a continuum of ND (3–5). Other overlap ND include pustular eruptions of ulcerative colitis, bowel bypass syndrome and rheumatoid neutrophilic dermatosis (4). Several patients with atypical forms of ND have been reported (3–5), but only a few cases of ND which could not be categorized as classic or atypical have been described. These unclassified ND can present with papules, nodules, pustules and/or ulcers, and often occur in patients with myeloid malignancies (3, 15, 16).

The patient described in this report had RAEB and developed two distinct types of ND after erythropoietin administration for severe anaemia. The first ND consisted of a symmetrical papular eruption that occurred 3 months after initiation of erythropoietin therapy and resolved rapidly following drug withdrawal and without active treatment. The second ND had the typical clinical and histologic features of EED and developed while the first eruption was healing. EED responded to a brief course of dapsone therapy. Several cases of ND have been attributed to an adverse reaction to drugs (6). Most cases had the typical features of Sweet’s syndrome, and only a few cases of drug-induced pyoderma gangrenosum have been reported (6–10). Granulocyte colony-stimulating factor (G-CSF) is the most commonly reported agent (11, 14). Other medications associated with ND are trimethoprim-sulfamethoxazole, minocycline, nitrofurantoin, furosemide, hydralazine, celecoxib, oral contraceptives, pneumococcal vaccin and bacillus Calmette-Guerin vaccine (6–10). Most of the ND attributed to G-CSF have been observed during treatment of chemotherapy-induced neutropenia in patients with myeloproliferative disorders, solid tumours or aplastic anaemia. The duration of therapy before ND onset varied between a few days of starting treatment and 2 years, and skin lesions resolved spontaneously within 30 days of drug cessation (11, 13). It is possible that G-CSF which usually promotes the differentiation, activation, maturation and chemotaxis of neutrophils may accidentally induce cutaneous proliferation and/or accumulation of neutrophils in predisposed patients. The presence of high serum levels of G-CSF in a patient with Sweet’s syndrome and myeloproliferative disease may support this hypothesis (11). To our knowledge, there is only one previous report of a ND developed after treatment with erythropoietin. A haemodialized patient treated with subcutaneous erythropoietin developed pyoderma gangrenosum at the site of injection on the day after beginning the therapy, and skin lesions resolved completely with systemic steroids 3 weeks later (17).

The association of typical and atypical ND, occurring simultaneously or separately, with myelodysplastic syndromes has been described repeatedly (16, 18). ND may herald or follow the diagnosis of myeloid malignancies and seem to be associated with a poorer prognosis. Moreover, four cases of ND associated with

![Fig. 2. Nodular violaceous lesions on the extensor surface of elbows (photo), knees and fingers appeared while the papular eruption was healing.](image-url)
myelodysplastic syndromes and resolved spontaneously have been reported (16). These include one patient with Sweet’s syndrome, two with unclassified ND and one with neutrophilic eccrine hidradenitis. Also the course of EED is unpredictable because nodules may persist for many years or regress spontaneously (19). Although in our patient the onset of unclassified ND and EED could be related to the underlying myeloid disease, the rapid resolution of the skin lesions following erythropoietin withdrawal points to a causative role of the drug.

REFERENCES