Bullous Pyoderma Gangrenosum Associated with Hairy Cell Leukemia and Its Complete Response to Cladribine Therapy

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Abstract Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis seen in association with systemic disorders including hematologic malignancies. Hairy cell leukemia (HCL) however, is an unusual association of PG. We describe a 49-year old lady who presented to our hematology clinic with easy fatigability and ulcerative skin lesions of 6 months duration. Examination revealed pallor and massive splenomegaly. Indurated, ulcerated lesion with undermined edges and necrotic base was

observed on left thigh. Investigations revealed pancytopenia and bone marrow examination identified typical hairy cells. Flow cytometry of marrow aspirate was suggestive of classical HCL. BRAF V600E mutation was detected in peripheral blood by reverse transcriptase polymerase chain reaction. Skin biopsy revealed neutrophilic dermatosis and findings classical of bullous PG. Cladribine therapy (0.09 mg/kg/day by continuous intravenous infusion for 7 days) led to remission of both HCL and PG after a duration of 4 weeks. Cladribine monotherapy in a case of PG with HCL may avoid the additional immunosuppression risk imposed by treating PG separately with corticosteroids. Immunosuppressive role of cladribine might be helpful in treating PG concurrent with HCL.

Keywords Pyoderma gangrenosum · Hairy cell leukemia · Cladribine · Immunosuppression

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Hairy cell leukemia (HCL) is a rare hematological malignancy (2–3 % of all leukemias) [1]. Although cutaneous lesions (10–12 %) in the form of vasculitis are seen in HCL, pyoderma gangrenosum (PG) is rarely reported [1]. A 49-years old lady presented to our hematology clinic with easy fatigability, early satiety and ulcerative skin lesions on both thighs since 6 months. Examination was remarkable for pallor, hepatomegaly (3 cm) and splenomegaly (10 cm). Skin examination revealed an erythematous plaque with central bulla and violaceous periphery (Fig. 1a) on posterior aspect of right thigh. An indurated plaque with central ulcer having undermined violaceous edges and a necrotic base was identified on anterolateral aspect of left thigh (Fig. 1b). Investigations revealed Hb-82 gm/l, white cell count— $1.5 \times 10^9/l$, differential counts: 17 % polymorphs, 82 % lymphocytes, 1 % monocytes and

Fig. 1 Above two panels Clinical photograph of the patient showing an erythematous plaque with central bulla and violaceous periphery on posterior aspect of right thigh (**a**, upper left) and an indurated plaque with central ulcer having undermined violaceous edges and necrotic base on anterolateral aspect of left thigh (**b**, upper right).

Below two panels

Photomicrograph showing bulla at dermo-epidermal junction and bulla cavity contains fibrinous material (H and E, $\times 100$; below left, **c**) and photomicrograph showing superficial dermal necrosis with perivascular neutrophilic infiltrate consistent with bullous pyoderma gangrenosum (H and E, $\times 200$, below right, **d**)

platelets— $90 \times 10^9/l$. Bone marrow biopsy was hypercellular with sheets of lymphocytes having hairy cell morphology and giving a ‘fried egg’ appearance (Fig. 2). Flow cytometry was positive for CD19, CD22, CD25, CD11c, CD123, CD103, FMC7 and CD79b and negative for CD5, CD23, CD4 and CD8. BRAF V600E mutation

was detected by reverse transcriptase-polymerase chain reaction in the peripheral blood. Skin biopsy findings (from left thigh lesion) were consistent with bullous pyoderma gangrenosum (Fig. 1c, d). Cladribine therapy (0.09 mg/kg/day by continuous intravenous infusion for 7 days) led to complete remission of the hairy cell leukemia and

Fig. 2 Photomicrograph of the peripheral blood smear showing atypical lymphocytes with irregular nuclear membrane, inconspicuous nucleoli, clumped chromatin, scant cytoplasm and hair like projections: typical hairy cells (H and E, $\times 1000$) (**a**, **b**). Bone marrow trephine biopsy showing diffuse infiltration by hairy cells ($\times 200$) (**c**) and a typical “fried egg appearance” ($\times 400$) (**d**)

resolution of skin lesions (assessed after 4 weeks of therapy). PG is a rare neutrophilic dermatosis (3 per million people per year) seen most often (50–70 % cases) in association with systemic disorders like inflammatory bowel disease, hematologic disorders and arthritis [2]. Myelodysplastic syndrome, acute myeloid leukemia, myeloma, monoclonal gammopathies, lymphoma, leukemia, myelofibrosis, large granular leukemia and myeloproliferative disorders are amongst the common hematological associations of PG [3, 4]. No case of PG was observed by Finan et al. [5] in their review of 113 cases of HCL. Since its first recognition by Crow and Bowers [6], only few cases of PG have been reported thereafter in association with HCL. Notably, Tombak et al. [2] recently reported a case of PG diagnosed concurrently with HCL and managed successfully with cladribine. Pathogenesis of PG is poorly understood although immune dysregulation plays a dominant role especially involving neutrophil chemotaxis. Role of tumor necrosis factor alpha (TNF- α) in promoting neutrophil infiltration has been postulated. Consistent with this, corticosteroids are mainstay of therapy for PG followed by other immunosuppressive agents (cyclosporine, azathioprine, mycophenolate, Cyclophosphamide, dapsone, minocycline) as well as biological (TNF- α antagonists) [4]. Cladribine is a cell cycle non-specific and potentially myelosuppressive and immunosuppressive nucleoside analogue acting on both resting and dividing lymphocytes [7]. Although, treatment of PG requires aggressive immunosuppressive therapies, their use in patients of HCL receiving cladribine may further add to the risk of acquiring opportunistic infections. Present case highlights the fact that in the setting of concurrent PG and HCL, cladribine alone might be able to achieve remission of both the conditions thereby avoiding the additional immunosuppression risk posed by treating PG separately by corticosteroids. Immunosuppressive properties of cladribine may be responsible for its efficacy in PG associated

with HCL. Need for biopsy of cutaneous lesions to rule out vasculitis or hairy cell infiltration and role of cladribine in treatment of PG associated with HCL is also highlighted.

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Compliance with Ethical Standards

Conflicts of interest The authors do not have any conflicts of interests to disclose.

Consent The authors state that written consent was obtained from the patient prior to publication of any material relating to him.

Ethical Clearance The authors declare that the article follows the required ethical standards as per Helsinki's declaration.

References

1. Svecová D, Pallová A, Chmurová N, Babal P (2008) Paraneoplastic vasculitis associated with hairy cell leukemia. *Prague Med Rep* 109:83–87
2. Tombak A, Aygun S, Serinsoz E, Tiftik EN (2015) Complete recovery of pyoderma gangrenosum after successful treatment of underlying hairy cell leukemia with cladribine. *Korean J Intern Med* 30:739–741
3. Bhat RM (2012) Pyoderma gangrenosum: an update. *Indian Dermatol Online J* 3:7–13
4. Saigal R, Singh Y, Mittal M, Kansal A, Maharia HR (2010) Pyoderma gangrenosum. *J Assoc Phys India* 58:378–383
5. Finan MC, Su WP, Li CY (1984) Cutaneous findings in hairy cell leukemia. *J Am Acad Dermatol* 11:788–797
6. Crow KK, Bowers RE (1974) Bullous haemorrhagic ulceration, a variant of pyoderma gangrenosum. *Trans St Johns Hosp Dermatol Soc* 60:142–151
7. Sigal DS, Miller HJ, Schram ED, Saven A (2010) Beyond hairy cell: the activity of cladribine in other hematologic malignancies. *Blood* 116:2884–2896