Erythema nodosum leprosum mimicking Sweet’s syndrome: an uncommon presentation

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Accepted for publication 22 October 2014

Summary  Erythema nodosum leprosum (ENL) lesions may uncommonly develop ulceration, necrosis, pustulation or bullae. This 60-year-old female was hospitalised with previously undiagnosed multibacillary (BL) leprosy and Sweet’s syndrome-like ENL, a presentation that is rarely reported. In addition to skin lesions simulating Sweet’s syndrome, she had anaemia, elevated ESR, and a peripheral leucocytosis with neutrophilia, the laboratory features of Sweet’s syndrome. The final diagnosis was made from chronic iridocyclitis, presence of lepra bacilli in slit-skin smears, and histology. The pathogenesis of Sweet’s-like ENL remains conjectural. In Sweet’s syndrome a complex interplay of various cytokines leading to an abundance of pro-inflammatory cytokines in the target tissues has been postulated to initiate an abnormal tissue response to certain antigens; such findings may eventually explain these uncommon lepra reactions as well.

Introduction

Erythema nodosum leprosum (ENL) or Type-2 lepra reaction is an immune complex (Type-III, Coomb’s and Gel hypersensitivity) mediated immune reaction that is more likely to occur in the lepromatous part of the leprosy spectrum during or after release from treatment. However, in rare instances it may occur before treatment, especially among patients experiencing stress, hormonal changes, coexisting infections or treatment with broad-spectrum antibiotics such as ofloxacin, rifampicin or other macrolides. It is characterised by recurrent crops of widespread superficial or deep, erythematous, inflamed papules and nodules associated with fever, malaise, arthralgia, peripheral oedema and/or other systemic complications. ENL lesions with ulceration, necrosis, pustulation or bullae are uncommon.
ENL lesions mimicking those of Sweet’s syndrome are rarely reported. Sweet’s syndrome (SS) or acute febrile neutrophilic dermatosis presents typically with abrupt onset of erythematous, tender, papulo-nodulo-plaques with or without pseudovesiculation. Associated constitutional symptoms of fever and malaise are frequent. Neutrophilic dermal infiltrate and leucocytoclastic vasculopathy on histology, peripheral leucocytosis with neutrophilia (> 70%) and a good therapeutic response to systemic corticosteroids are its hallmark features (Table 1).

Nearly 20% of these patients have associated malignancies (hematologic disorders account for > 85%), while infections (viral, bacterial, tuberculous and non-tuberculous mycobacterial), inflammatory bowel disease, drugs and pregnancy are more likely associated disorders in others. We report here a patient with ENL lesions simulating Sweet’s syndrome.

Case Report

This 60-year-old, HIV-negative, female had developed multiple, painful, erythematous and oedematous plaques (a few with erosions) of variable size (3–5 cms) over face, forearms, back, buttocks and thighs 5 days previously. She had redness/smarting of eyes, and episodes of fever and malaise. She described these lesions being larger, more painful, persisting, and different from the earlier ones she had during four episodes in the past 2 years. She had received treatment from a peripheral centre during these years but had no records with her. These lesions were erythematous, warm, tender, and a few had a target appearance suggestive of Sweet’s syndrome morphologically (Figure 1).

She was febrile (temp 38.8°C) and had pallor, facial swelling, and a few widespread erythematous nodules. Pending investigations she was treated with prednisolone (40 mg/d) and showed improved general wellbeing within 2–3 days. Ophthalmic examination showed

Table 1. Diagnostic criteria for Sweet’s syndrome

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| Classic Sweet’s syndrome | 1. Abrupt onset of painful erythematous plaques or nodules  
2. Histopathologic evidence of dense neutrophilic infiltrate without evidence of leucocytoclastic vasculitis |
| Minor | 1. Pyrexia > 38°C (100.4°F)  
2. Association with an underlying hematologic or visceral malignancy, inflammatory disease, pregnancy, or preceded by an upper respiratory or gastrointestinal infection, or vaccination  
3. Excellent response to treatment with systemic corticosteroids or potassium iodide  
4. Abnormal laboratory values at presentation (three of four): erythrocyte sedimentation rate > 20 mm/hr, positive C-reactive protein, > 8000 leukocytes, > 70% neutrophils |
| Drug-induced Sweet’s syndrome | 1. Abrupt onset of painful erythematous papules or nodules  
2. Histopathologic evidence of dense neutrophilic infiltrate without evidence of leucocytoclastic vasculitis  
3. Pyrexia > 38°C (100.4°F)  
4. Temporal relationship between drug ingestion and clinical presentation or temporally related recurrence after oral challenge  
5. Temporally related resolution of lesions after drug withdrawal |

Notes: Presence of both major and two of the four minor criteria is required to establish the diagnosis of Classic Sweet’s syndrome. All five (A, B, C, D and E) are required for the diagnosis of drug-induced Sweet’s syndrome.
an irregular shaped pupil and posterior synechiae formation in right eye, and cells in anterior
chamber of both the eyes. Both ulnar nerves were non-tender, asymmetrically and uniformly
thickened. There was no sensory or motor deficit. Laboratory investigations revealed
normocytic hypochromic anaemia (haemoglobin, 6·7 g%), leucocytosis (total leucocytes
18,700/mm³), neutrophilia (90%), and elevated erythrocyte sedimentation rate (ESR, 48 mm
in the first hour, normal value 5–10 mm in the first hour by Westergren method). Blood
biochemistry, C-reactive protein, anti-streptolysin-O (ASO) titres, chest x-ray, ultrasono-
graphy for abdomen/pelvis, and urinalysis were normal. A slit-skin smear examination
showed lepra bacilli (bacterial index (BI) of 6 + and a morphological index (MI) of 5%).
Histology of a forearm plaque showed an unremarkable epidermis, occasional epitheloid cell
granulomas, neutrophilic infiltration, vasculitis/vasculopathy, occasional neutrophilic
abscesses in the dermis and many lepra bacilli on Fite-Faraco staining. With the final
diagnosis of borderline lepromatous (BL) leprosy with ENL (Sweet’s syndrome-like lesions)
treatment with WHO MDT-MB was initiated along with prednisolone (40 mg/d). She was
also put under ophthalmological care for chronic iridocyclitis. Her general wellbeing
improved and the skin lesions subsided during the next 4 weeks of hospital stay. She was
discharged on tapering doses of prednisolone (reducing by 10 mg every 4 weeks). She was
taking prednisolone 10mg/d along with WHO MDT-MB at the last follow up and was free of
ENL lesions (Figure 2).

Discussion

ENL lesions, especially in the borderline spectrum of leprosy, have been described rarely to
mimic Sweet’s syndrome causing a diagnostic dilemma, particularly in previously
undiagnosed leprosy cases.2 Most of these reports recommend that it is considered as an
uncommon subtype of Type-2 lepra reaction, while also considering Sweet’s syndrome.\textsuperscript{2,3} Although iritis may occur occasionally, conjunctivitis, episcleritis and limbal nodules are \textit{bona fide} ocular manifestations of Sweet’s syndrome. Our patient had characteristic skin lesions, associated symptoms and a rapid response to systemic corticosteroids suggestive of Sweet’s syndrome both clinically and histologically. However, demonstration of lepra bacilli in slit-skin smears and histology was diagnostic. Although the exact nature of her past treatment could not be ascertained, it is likely that she had received broad-spectrum antibiotics prescribed routinely at peripheral centres, perhaps precipitating ENL. However, it is not unusual for borderline leprosy cases to present clinically with concurrent painful oedematous plaques and nodules, as in this case, suggestive of coexisting Type-1 and Type-2 lepra reactions. The important distinguishing histological features\textsuperscript{4} of Type-1 lepra reaction are intense dermal oedema, disorganised granuloma formation, marked lymphocytic infiltrate with few scattered neutrophils and Langhans’ giant cells. On the other hand, vasculitis is the predominant feature in some ENL cases, and most lesions will show dense infiltration by neutrophils in superficial/deep dermis and/or subcutis superimposed on pre-existing lepromatous granulomas. However, variable epidermal changes (hyperkeratosis, parakeratosis, acanthosis, flattened rete pegs, oedema, spongiosis, and occasionally basal cell degeneration, exocytosis, and subcorneal pustule), moderate to dense, perivascular, periadenexal neutrophilic dermal infiltrate, and vasculopathy (vascular dilatation, endothelial oedema, extravasation of erythrocytes) are highly characteristic of Sweet’s syndrome while true leukocytoclastic vasculitis occurs occasionally.\textsuperscript{1} Interestingly, the features of neutrophilic lobular and/or septal panniculitis, as in ENL, are also seen in the subcutaneous variety of Sweet’s syndrome and needs differentiation from other dermatoses with similar histology (alpha 1-antitrypsin deficiency, factitial panniculitis, infection, leucocytoclastic vasculitis, pancreatitis, and rheumatoid arthritis).\textsuperscript{5}

\textbf{Figure 2.} Histology from a forearm plaque shows unremarkable epidermis, granulomatous inflammation in the dermis (a, H&E $\times$ 10), epitheloid cell granuloma, vasculitis/vasculopathy, and neutrophilic infiltration extending to subcutis (b, H&E $\times$ 40), and many lepra bacilli in tissue sections (c, Fite-Faraco $\times$ 100).
The aetio-pathogenesis of Sweet’s syndrome remains obscure and is considered to be a hypersensitivity phenomenon. A complex interplay of cytokines leading to an abundance of pro-inflammatory cytokines, especially IL-1, G-CSF, GM-CSF and IFN-α in the target tissues has been postulated to initiate an abnormal tissue response to certain antigens. However, the characterisation of the pathomechanisms involved in such unusual phenomenon in ENL will perhaps be speculative as of now. The simultaneous occurrence of Sweet’s syndrome and erythema nodosum, a hypersensitivity septal panniculitis, is also well documented and the possibility of immune complex formation as a common initiating factor in both disorders has been suggested. Interleukin (IL)-8 reactive dendritic cells in the dermis of Sweet’s syndrome cases has been demonstrated. Elevated serum levels of IL-6 and granulocyte-colony stimulating factor (G-CSF) during the acute phase of Sweet’s syndrome, increased IL-1 production by acute myelogenous leukaemia (the commonest malignancy associated with Sweet’s syndrome) cells, and its recurrence after G-CSF therapy all indicate the possible pathogenic role of these mediators in Sweet’s syndrome. There is also indirect evidence suggesting an increased CD4+ lymphocyte activity in ENL. Evidence is also gathering towards modulating action exerted by the neutrophils on dendritic cell function and that of T-cell subsets in turn. Mycobacterium leprae infected neutrophils also perhaps interact with dendritic cells and increase IL-2, possibly IL-17, and newer T-helper 17 (TH17) subset. Although the exact role of these events in the pathogenesis of Sweet’s-like ENL remains conjectural, such findings may eventually help to explain such uncommon lepra reactions.

Acknowledgements

The help extended by our colleagues from the department of pathology in histopathology reporting is gratefully acknowledged. We are also thankful to the patient for her consent and cooperation in bringing out this report.

References

ENL mimicking Sweet’s syndrome


