CASE REPORT

Erythema necroticans: A presenting manifestation of silent leprosy

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Abstract
Leprosy reactions are rare expression of immunological perturbations that interrupt the usual chronic course and the clinical stability of patients with leprosy. Erythema nodosum leprosum (ENL) is an immune complex-mediated reaction that may complicate the course of multibacillary leprosy. It generally occurs during antimycobacterial treatment and characterized by the appearance of crops of brightly erythematous tender nodules or plaques. Severe ENL can become vesicular or bollous and break-down and is termed erythema necroticans (Jobling, W.H., Mc Dougall, A.C., 1996. Leprosy reactions. In: Handbook of leprosy, 5th ed. CBS Publishers, New Delhi, pp. 82–91). We present here a case of erythema necroticans, misdiagnosed as sweet’s syndrome, because he had never been presented with pre-existing evidence of leprosy nor had any antimycobacterial treatment. The clinical diagnosis is confirmed by microscopic pathology. The lesions resolved completely following multibacillary MDT, corticosteroids and Azathioprine.

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1. Introduction

Leprosy is a disease of slow development that presents a wide spectrum of clinical, histopathological and immunological characterization. Leprosy reactions are rare and not well-known states that interrupt the usual chronic course and the clinical stability of patients with leprosy. They are expression of immuno-

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2. Case report

A 44 years old diabetic male from Indonesia, was referred from a private clinic for management of recurrent attacks of
severe and extensive painful skin lesions associated with fever and deteriorating general condition. He has been diagnosed clinically as Sweet’s syndrome and received monthly injections of steroids during the past one year to control the attacks. On examination, the patient had fair general condition, cushingoid features. There are multiple geographic brownish macules all over his trunk and extremities. The condition was diagnosed as postinflammatory hyperpigmentation and treated as such. The patient has been advised to return to the clinic with any new lesion. Within one month, the patient came to the clinic by wheel chair. He presented with high grade, intermittent fever, with other systemic symptoms such as, bone tenderness, myalgia, ankle and knee arthralgia, neuritis, edema and malaise. He developed crops of painful skin lesions all over the body including the face over a few days. He had similar recurrent episodes during the last 12 months. The patient had never presented with chronic skin lesions or neurologic deficit suggestive of leprosy. On admission, he was found having cushingoid features. There were multiple painful erythematous tender nodules, erythema multiform-like lesions and skin necrosis of various sizes present over the trunk and extremities, several of them with flaccid blister, sometime hemorrhagic or seropurulent (Fig. 1A–E). The joints were mildly swollen and tender. The ulnar, lateral popliteal and great auricular nerves were thickened. Histopathologic analysis showed poorly defined epithelioid granulomas with lepra cells and numerous inflammatory cells including neutrophils, lymphocytes and rare eosinophils centered around blood vessels, nerves and adnexal structure occupying the superficial, mid and deep dermis (Fig. 2A–C). Fite stain shows numerous acid fast organisms (Fig. 3). Slit skin smear from the lesion showed BI of 3+, while IgM anti-phenolic glycolipid I (anti-PGL-I) findings were negative. All routine investigations were within normal limits except for raised ESR, C-reactive protein (CRP) and leukocytosis. Examination of other systems reveal high liver enzymes, otherwise it was unremarkable. Ocular examination and chest X-ray did not reveal any abnormality.

The diagnosis of borderline lepromatous leprosy presentation with necrotic and bullous type eryhema nodosum leprosum was made. He started on (WHO) MB-MDT therapy along with 40 mg daily prednisolone. After improvement of general condition, the ENL reaction was controlled and the patient became asymptomatic. He was discharged after two weeks on (WHO) MB-MDT therapy and with gradual tapering of the prednisolone over one month and stopped. One month after stopping prednisolone, the patient developed a

Figure 1 (A–E) Multiple painful erythematous tender nodules. Erythema multiform like lesions and skin necrosis of varied sizes were present over the trunk and extremities, several of them with flaccid blister, sometime hemorrhagic or seropurulent.

Figure 2 (A–C) Histopathologic analysis showed poorly defines epithelioid granulomas with lepra cells and numerous inflammatory cells including neutrophils, lymphocytes and rare eosinophils centered around blood vessels, nerves and adnexal structure occupying the superficial, mid and deep dermis.
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Figure 3  Fite stain shows numerous acid fast organisms.

recurrent severe attack of ENL, with extensive skin lesions associated with fever and joint pain. The dose of prednisolone increased to 80 mg daily orally for 2 weeks. But, there was no adequate control of ENL with this treatment, moreover, he continued to develop new lesions with persistence of the fever and joint pain. Second-line drug such as Thalidomide has been suggested. Thalidomide was not available in our center. The patient was treated with (WHO) MB-MDT, prednisolone reduced to 40 mg daily. Azathioprine was added at a dose of 100 mg daily (2 mg/kg /day). ENL lesions started healing with complete relief within 4 weeks. Prednisolone was reduced by 10 mg every week and then stopped after 4 weeks, while Azathioprine 50 mg daily was continued for 6 months then stopped. Complete blood count, liver and renal function tests were repeated every month during the azathioprine treatment which remained unremarkable. The ENL never recurred.

3. Discussion

Erythema nodosum leprosum (ENL) is an immune complex-mediated reaction that may complicate the course of multibacillary leprosy and characterized by the appearance of crops of brightly erythematous tender nodules or plaques. Severe ENL can become vesicular or bullous and break-down and is termed erythema necroticans (Jobling and Mc Dougall, 1996). The small number of reported cases in the world literature suggests that it is fairly uncommon (Verma and Pandhi, 1993; Davis et al., 2002; Pandhi et al., 2005; Athanasia et al., 2008; Zannatun et al., 2009). Our patient shows polymorphic lesions clinically, less nodular than classical ENL, which is mainly seen in the trunk, but has more erythematous, or violaceous macules and plaques distributed on the extremities. The plaques have vesicles, bullae and necrotic skin.

Although erythema nodosum leprosum occurs usually during the treatment of lepromatous leprosy, there have been a fair number of reports of untreated lepromatous leprosy with subtle initial changes, presenting de novo as ENL, or may present with extraordinary manifestations, often with long delay before the diagnosis of leprosy is considered (Zannatun et al., 2009; Mc Dogall and Archibald, 1977). Here, we describe a case present with necrotic ENL as presenting manifestation of subtle borderline lepromatous leprosy; he had no previous evidence of neurologic deficit or chronic skin lesions suggestive of this chronic infection. The condition was difficult to diagnose clinically; numerous tender nodules and plaques and necrotic lesions with seropurulent blisters led to the initial misdiagnosis of Sweet’s Syndrome. But, what provokes the subtle leprosy from its dormant to express ENL reaction? The probable trigger factors associated with ENL reaction include surgical operations, pregnancy, parturition, lactation, menopause, trauma, intercurrent illness, vaccination, physical or mental stress and some time therapy (Verma and Pandhi, 1993; Zannatun et al., 2009). Tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine, plays an important role in the pathogenesis of ENL. There is activation of T-cell and macrophages, inducing production of large amounts of TNF-α (Kaushal et al., 2006). Additional source of TNF-α is the severe leukocytosis and the intense neutrophil infiltrate in ENL lesions. Plasma levels of this cytokine have been found to be high during the episode of ENL (Sehgal et al., 1988). High CRP levels along with a positive correlation between elevated TNF-α and CRP levels in the serum of ENL patients has been reported (Foss et al., 1993). In the present case, the patient presented with high serum level of CRP that regressed by the end of the attacks. Taken together, leukocytosis, TNF-α and CRP could be considered as laboratory parameters to be used to follow up the acute inflammatory response in ENL (Foss et al., 1993). The management of ENL is a real challenge for clinicians; ENL has usually a relapsing and remitting course that may last for several years. ENL produce greater disability than the underlying lepromatous leprosy and was the commonest reason for admission to the hospital (Levy et al., 1973). Three types of ENL were identified: single acute ENL, multiple acute ENL (repeated discrete episodes) and chronic ENL (continuous episodes). 92% of ENL reactions are usually chronic and relapsing with unpredictable clinical course (Eonor et al., 2006). Our patient has almost nine recurrent episodes of ENL during the last 12 months. Multiple drug therapy (MB-MDT) for borderline lepromatous leprosy should preferably be taken as per the recommendations of WHO (Eonor et al., 2006). In addition, treatment with prednisolone should be instituted for 12 weeks course. This overlooks the chronic, recurrent nature of ENL (WHO, 1998). Although prednisolone is used as the first-line drug for treating moderate and severe ENL, its effect in managing patients with ENL is less than adequate (Eonor et al., 2006). The WHO has recommended the antiinflammatory clofazimine for chronic and severe ENL and as steroid-sparing agent (Pannikar, 2003). However, it takes 4–6 weeks for the effect of clofazimine to be clinically detectable. Thus, it is not useful for the management of acute ENL (Eonor et al., 2006; WHO, 1998). Clofazimine 100 mg tablets are available only in MDT blister packs for the patients in our center.

Thalidomide is now considered the drug of choice for ENL. It was approved by the FDA in 1998 in the acute treatment of moderate to severe ENL and preventing new episodes (www.fda.gov). There are serious limitations to its use due to its teratogenic effects and potential neurotoxicity, causing it to be banned in many countries (Pannikar, 2003). Our patient may have benefited from this drug, but it is not available in our center, and the cost is out of reach of the patient. The search for an effective alternatives, led to experiencing second-line drugs such as pentoxifyline (Sales et al., 2007), mycophenolate mofetil (Kalian and Raghubir, 2008), Azathioprine (Kaushal et al., 2006) and infliximab (Williamie et al., 2006) with inconsistent results. We have chosen Azathioprine for our patient because it has strong antiinflammatory effect and has also been shown to inhibit TNF-α. The drug has been effectively used on long-term basis as a steroid-sparing agent. Its long-term safety, adverse effects and monitoring have been well studied (Kaushal et al., 2006).
4. Conclusion

We report this case because experience shows that in non-endemic areas such as State of Qatar and with the growing number of immigrants arriving for work, diagnostic dilemma posed in correctly identifying patients with chronic infectious diseases such as leprosy, lead to long delay before the correct diagnosis was considered, and subsequently the use of inappropriate therapies such as corticosteroids, which can potentially worsen the disease. Practicing physicians need to have a high clinical index of suspicion and to be aware of the extraordinary presentation of the different chronic infectious diseases that make them hard to diagnose.

References


