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Case Report

Role of Cyclophosphamide as a Glucocorticosteroid Sparing Agent in a Case of Erythema Necroticans

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Erythema necroticans (ENe) is a severe ulcero-necrotic form of erythema nodosum leprosum (ENL). It usually occurs during the phase of multidrug therapy for leprosy, though it can occur spontaneously too. It is difficult to diagnose and treat the atypical forms of ENL, especially when they are the presenting symptoms of a leprosy patient. The preferred treatment options are systemic glucocorticosteroids (GCS), thalidomide and clofazimine. In cases of ENL and diabetes mellitus (DM), management of DM is complicated by using high-dose GCS in such patients. Herein, we report a 48-year-old female, who presented with multiple painful skin lesions over face, chest, abdomen, back, bilateral upper limbs and lower limbs for 10 days. Slit skin smear was found to be positive. Histopathological findings were suggestive of ENe. She was then started on WHO adult multibacillary anti leprosy pack, injectable GCS and ceftriaxone, but on regular monitoring there was a rise in her blood sugar level. Taking into account possibility of GCS induced DM, introduction of steroid sparing agent became mandatory. Cyclophosphamide was prescribed on feasibility ground and GCS was gradually tapered. The patient improved on follow-up after 1 month with healing of ulcers. This report highlights the role of oral Cyclophosphamide as a steroid sparing agent for treating ENe.

Keywords: Leprosy, Erythema Nodosum Leprosum, Erythema Necroticans, Glucocorticosteroid, Cyclophosphamide

Introduction

Mycobacterium leprae causes leprosy, a chronic granulomatous infectious illness that can present with a variety of clinical symptoms. It is a significant challenge faced by developing and underdeveloped countries, as it causes disability and morbidity, and adversely impacts the quality of life of affected individuals (Alfieri et al 2024).

Erythema nodosum leprosum (ENL), a Type II lepra reaction, is classically characterized by the presence of painful subcutaneous nodules along with constitutional symptoms (fever, malaise, arthralgia and myalgia) as well as neuritis, uveitis, orchitis or involvement of other organ systems. Atypical cutaneous manifestations of ENL include pustular, hemorrhagic, and erythema multiforme-like lesions, as well as the more severe form of necrotic ulcerative lesions known as Erythema necroticans (ENe). It usually occurs

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during the phase of multidrug therapy, though it can occur spontaneously too (Panigrahi et al 2020).

It is difficult to diagnose and treat the atypical forms of ENL, especially when they are the presenting symptoms of leprosy. The preferred treatment options are systemic glucocorticosteroids (GCS), thalidomide and clofazimine. Management of diabetes mellitus (DM) is complicated by using high-dose GCS in such patients. ENe has strong component of vasculitis. Immunosuppressants like azathioprine, methotrexate, cyclophosphamide are useful in management of vasculitis as a steroid sparing agent.

An attempt was made to study the efficacy of cyclophosphamide in a case having ENe with GCS induced DM.

Case Report

A 48-year-old, married female presented with complaints of multiple painful skin lesions over face, chest, abdomen, back, bilateral upper limbs, and lower limbs for 10 days. The lesions were sudden in onset, initially on abdomen, chest, face and then rapidly progressed to involve whole of the body. She also had complaints of evening rise of the temperature, which was low-grade and intermittent in nature. She took treatment from a private hospital and was started on capsule rifampicin (600mg) once a month, tablet dapsone (100mg) once a day and tablet prednisolone(10mg) once a day.

Table 1: Differentiating features between Erythema Necroticans, Pyoderma Gangrenosum and Lupus Panniculitis

	Erythema Necroticans	Pyoderma Gangrenosum	Lupus panniculitis
Etiopathogenesis	Severe manifestation of Type 2 Lepra reaction	Idiopathic neutrophilic vasculitis often associated with autoimmune/ inflammatory conditions	Form of cutaneous lupus erythematosus that can be a manifestation of Systemic lupus erythematosus
Clinical features	Painful,ulcerated and necrosed nodules and plaques	Painful pustules,nodules or ulcers usually with undermined and violaceous borders.	Red,tender nodules and plaques which may ulcerate and leave scarring
Characteristic histopathological findings	Dermis shows presence of perivascular, periadnexal and interstitial inflammatory infiltrates comprising mainly of lymphocytes, plasma cells, few neutrophils and foamy histiocytes.	Dermis contains dense neutrophilic infiltrate and signs of vasculitis. Immune complex deposits are found in the vessel walls of the dermis.	Dermis shows lymphocytic infiltrate. Fat necrosis and hyaline degeneration are also seen.

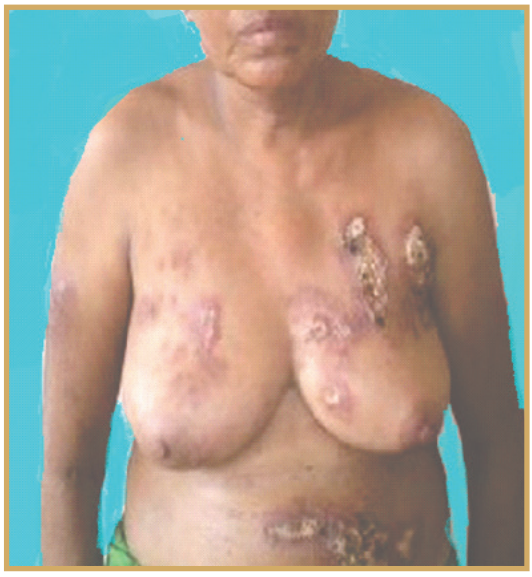

Fig. 1a: Multiple well-defined erythematous, crusted necrotic plaques over chest, abdomen.

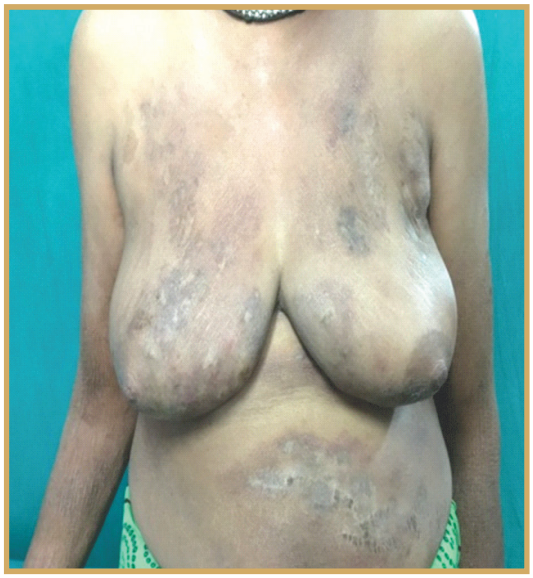

Fig.1b: Multiple healed atrophic and hyperpigmented scars on chest and abdomen.

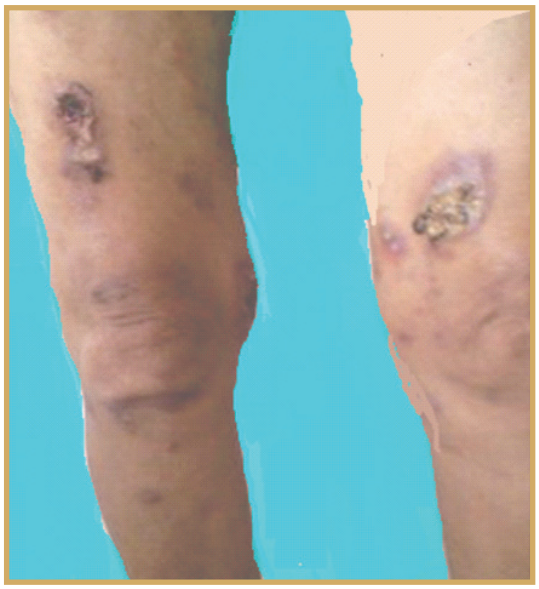

Fig. 2a: Multiple well-defined erythematous, crusted necrotic plaques over anterolateral aspect of bilateral lower limbs.

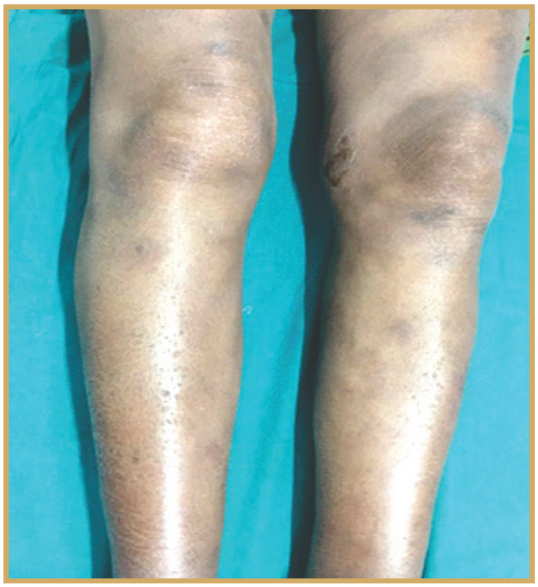

Fig. 2b: Healed atrophic and hyperpigmented scars on bilateral lower limbs.

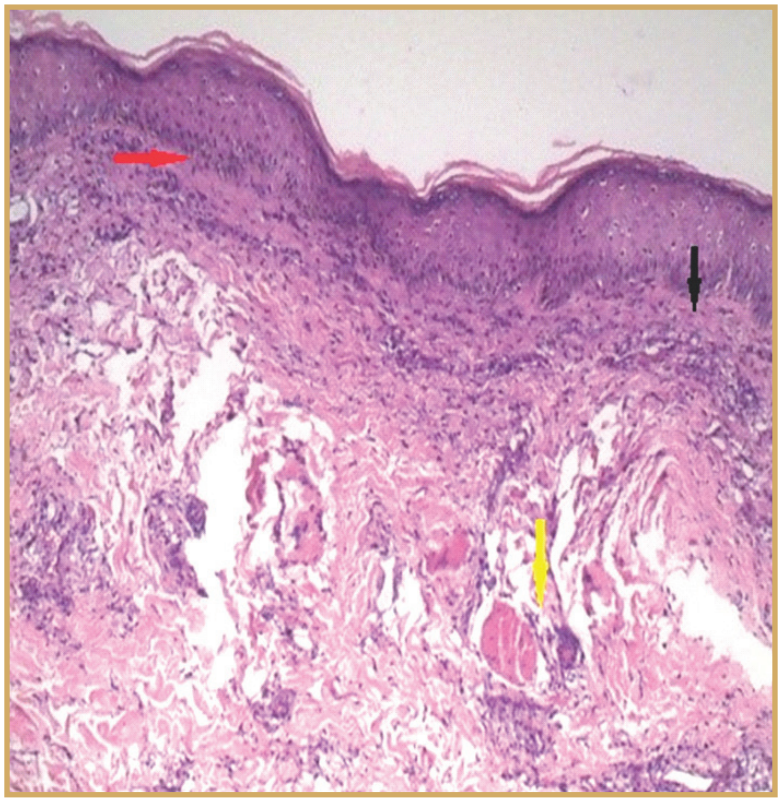

Fig. 3: Histopathology (Hematoxylin & Eosin stain, 40X): Epidermis shows flattening of rete ridges red arrow) and presence of grenz zone (black arrow). Dermis shows presence of perivascular, periadnexal and interstitial inflammatory infiltrates comprising of lymphocytes, plasma cells, few neutrophils and foamy histiocytes (yellow arrow).

On cutaneous examination, there were multiple well-defined erythematous, crusted necrotic plaques over chest, abdomen, back, buttocks, right shoulder, anterolateral aspect of bilateral lower limbs. Few erythematous nodules were present over face and neck (Figs. 1a & 2a). Bilateral ulnar and superficial radial nerves were thickened and non-tender. Sensations over hands and feet were intact. There were no motor changes.

Differential diagnosis considered were ENe, pyoderma gangrenosum, and lupus panniculitis (Table 1). On histopathological examination (Fig. 3) overlying epidermis showed flattening of rete ridges (red arrow) and presence of grenz zone (black arrow). Dermis shows the presence of perivascular, periadnexal and interstitial inflammatory infiltrates comprising of lymphocytes, plasma cells, few neutrophils and foamy histiocytes (yellow arrow). Wade-Fite stain was also positive. Final diagnosis of lepromatous Leprosy with ENe was considered.

On further Investigating the patient, her hemoglobin was 9.6gm%, total White blood cell count was 38,000/cumm, neutrophilia noted. Random blood sugar (RBS), Liver function test and

Renal function test were within normal range. AFB showed high bacillary load (Bacteriological Index Grade 3+). Chest X-Ray and USG abdomen revealed no abnormality**.**

Patient was started on WHO multibacillary anti leprosy pack comprising of 2 capsules of rifampicin (300mg×2) plus 3 capsules of clofazimine (100mg×3) plus 1 tablet of dapsone (100mg) as once a month dose and daily dose of 1 capsule of clofazimine (50mg) plus 1 tablet of dapsone (100mg). She was also started on injection dexamethasone 8mg IV once daily along with injectable ceftriaxone 1 gram IV twice daily. On regular monitoring, persistent rise of blood sugar was noted. Taking into account possibility of GCS induced DM, introduction of steroid sparing agent became mandatory. Cyclophosphamide was prescribed on feasibility ground. Other options like thalidomide were not considered because of resource restriction.

Initially cyclophosphamide (50mg) 2 tablets was given with 2 glasses of water in the morning. After 10 days, cyclophosphamide dose was escalated to 150 mg per day as laboratory parameters like complete blood count and urine routine microscopy was within normal limits. GCS was gradually tapered. Patient was initially started on injectable dexamethasone 8mg for 1 week, followed by 40mg of oral prednisolone as single morning dose, which was tapered gradually by 10mg every 15 days followed by a dose of 5mg of oral prednisolone maintained for 1 month. The patient improved on follow-up after 1 month with healing of ulcers (Figs. 1b&2b).

Discussion

ENe is a severe and uncommon vasculo-necrotic type of ENL, an immune complex-mediated reaction that makes multibacillary leprosy challenging to treat. Risk factors triggering ENe include patients having lepromatous leprosy (LL), high bacterial index, puberty, infection, vaccination, HIV, stress, surgery, trauma, malaria, tuberculosis, pregnancy, and breast-feeding (Panigrahi et al 2020). Ulcero-necrotic lesions associated with constitutional symptoms like fever, arthralgia, and myalgia are the presenting features. Occasionally, extracutaneous manifestations including neuritis, iridocyclitis, or orchitis may be seen. The absence of cardinal features like peripheral nerve thickening associated with neurologic deficit, patchy anaesthesia and slit skin smear positivity helps to rule out common differentials like furunculosis, cutaneous vasculitis, sweet's syndrome, polyarteritis nodosa, leishmaniasis, or malignant syphilis.

Lucio's Phenomenon (LP) is the most important differential diagnosis of ENe as it may also present with vasculo-necrotic reactions. LP usually develops between one to three years after the initial presentation of leprosy, in cases of untreated or incompletely treated non-nodular LL. Painful erythematous patches or plaques in the extremities are the earliest symptoms of LP, which later progresses to form necrotic ulcers having a geometric or jagged edge. However, no constitutional symptoms, neuritis and extracutaneous or systemic involvement are found in LP (Alfieri et al 2024).

GCS should be cautiously used as their continuous use leads to various side effects. Patients may develop steroid-dependence in cases of chronic, recurrent ENL. Studies have shown that persistent GCS use in ENL patients may lead to immunosuppression and fatal adverse effects such as septic shock, pneumonia, diabetic-ketoacidosis (Mishra et al 2024). Steroids should not be utilized to avert a new reaction, as this may lead to a dependence on steroids (Bhat & Vaidya 2020).

Other treatment options for ENL as documented by various research include, thalidomide,

methotrexate, clofazimine, pentoxifylline, cyclosporine, azathioprine, etanercept, colchicine, chloroquine, minocycline, and zinc (Zhu et al 2017).

In a study it was reported that after pulse therapy with cyclophosphamide, all cases showed total or partial regression of symptoms, and they were able to taper thalidomide and prednisone doses, with better control of ENL, thus avoiding further hospital admissions and disabilities (Machado et al 2023).

Cyclophosphamide is an alkylating agent having immunosuppressive and cytotoxic action. It specifically affects T cells and suppresses the immunity. Lower dosages have shown effect on the targeted immunomodulation of regulatory T cells, while higher doses are utilized in the treatment aimed at eliminating malignant hematopoietic cells. In the CSF and peripheral blood, it induces the release of Th2 cytokines such as IL-4 and IL-10 while reducing the secretion of interferon-gamma and IL-12 (Weir & Jan 2023, Payal et al 2024). It suppresses T and B cells and reduces antibodies, adhesion molecules, and cytokine production, hence reduces requirement of high dosages of GCS, hospitalizations, and disabilities.

Conclusion

First-line management of lepra reaction includes GCS, high-dose clofazimine, and thalidomide (Zhu et al 2017). It may not be feasible to prescribe high dose clofazimine and thalidomide in resource restricted setup. GCS sparing agents are necessary in cases having adverse drug reactions like DM, hypertension. In our patient, cyclophosphamide was preferred as there was a strong vasculitic component and because of its easy availability. Patient responded well and we were able to taper the GCS without recurrence.

A dearth of data on role of oral cyclophosphamide for the treatment of ENe prompted us to report this case.

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