www.jsstd.org

Journal of Skin and Sexually Transmitted Diseases

ScientificScholar® Knowledge is power
Publisher of Scientific Journals

IADVL 1973 KERALA

Net Case

Minocycline-induced acute generalized exanthematous pustulosis in a patient with lepromatous leprosy

Nikhila K. Narayanan[1], Mary Vineetha[1], Seena Palakkal[1], Payippat Leelamma Jayalakshmy[2], Lissy Skaria[1], Celine Machiyanickal Issac[3], T. K. Jaseela[2]

Departments of [1]Dermatology, and [2]Pathology, Government Medical College, Kottayam, [3]Department of Dermatology, Government TD Medical College, Alappuzha, Kerala, India.

***Corresponding author:**
Nikhila K. Narayanan,
Department of Dermatology,
Government Medical College,
Kottayam, Kerala, India.

nikhila.k.narayanan@gmail.com

Received: 06 November 2021
Accepted: 09 February 2022
EPub Ahead of Print: 18 May 2022
Published: 14 October 2022

DOI
10.25259/JSSTD_76_2021

Quick Response Code:

ABSTRACT

Cutaneous manifestations of leprosy are variable. It is a known fact that, in addition to the skin lesions related to the disease, multidrug therapy can also have an impact on patient's skin. In this report, we discuss a young girl with leprosy, who developed acute generalized exanthematous pustulosis to minocycline, which was given as an anti-leprosy drug.

Keywords: Acute generalized exanthematous pustulosis, Minocycline, Leprosy

INTRODUCTION

Leprosy can present with a wide variety of manifestations.[1,2] Pustular lesions, though not common, have been described as a manifestation of Type 2 lepra reaction.[3] Here, we report a case of minocycline-induced acute generalized exanthematous pustulosis (AGEP) in leprosy.

CASE REPORT

A 16-year-old girl presented with sudden eruption of pustules all over her body of 10 days duration which was associated with fever and chills. The lesions were pruritic.

The patient was receiving clofazimine 100 mg twice a day, minocycline 100 mg once a day, and ofloxacin 400 mg once a day for the past 4½ months for lepromatous leprosy and recurrent erythema nodosum leprosum (ENL). Earlier, she had received 1 year of multidrug therapy with rifampicin (600 mg once a month), clofazimine and ofloxacin (400 mg daily). Dapsone was substituted with ofloxacin as the patient developed dapsone-induced hemolytic anemia. Clofazimine was initiated at a dose of 50 mg daily and 300 mg once a month. However, after 8 months of anti-leprosy treatment, the daily dose of clofazimine was increased (100 mg, 3 times a day), since she started developing recurrent ENL. At the end of 1 year of treatment with rifampicin, ofloxacin, and clofazimine, the skin lesions persisted. The bacteriological and morphological indices were 6+ and 10, respectively. Hence, she was advised alternate regimen (clofazimine 50 mg daily, ofloxacin 400 mg daily, and minocycline 100 mg daily for the first 6 months followed by clofazimine 50 mg daily and ofloxacin 400 mg daily for 18 months),

suspecting drug resistance (as we did not have the facility to rule out the same). Clofazimine was given at 100 mg twice a day, instead of the recommended daily dose of 50 mg, since the management of ENL warranted a higher dose.[4]

Clinical examination revealed numerous, tender and non-follicular, tiny pustules distributed all over the body with relative sparing of the vault of axillae and cubital fossae [Figures 1a and b]. The underlying skin showed erythema and scaling. Axillary and inguinal lymph nodes were enlarged (1.5 × 1.5 cm) bilaterally. The enlarged nodes were firm, mobile, and non-tender. There were no mucosal lesions or any clinical evidence of organ involvement.

Peripheral blood examination showed neutrophilia (12,400 cells/mm^3 with 80% neutrophils). Liver and renal function tests were normal. Peripheral smear was within normal limits, except for the neutrophilia. Gram stain analysis of a pustule showed plenty of neutrophils without any organism.

We made a provisional diagnosis of drug-induced/infection-induced AGEP. All three drugs were withdrawn. We put her on cefotaxime 1 g intravenously 12th hourly and cetirizine 10 mg per orally once a day for 5 days. Pus and blood cultures were sterile.

The fever subsided. Skin lesions also showed complete resolution. After the subsidence of the lesions and the withdrawal of antihistamine, we restarted the anti-leprosy drugs one by one (one-fourth dose of a drug on day 1, half dose on the 2nd day, and full dose on the 3rd day. After 1 day, the next drug was added at one-fourth dose and the same schedule was repeated). The patient tolerated clofazimine and then ofloxacin. However, the patient developed recurrence of pustular eruptions and fever within 24 hours of administration of one-fourth dose of minocycline. The patient responded to withdrawal of minocycline and cetirizine given at a dose of 10 mg/day. Skin biopsy of a pustule showed well-formed, epithelioid cell granulomas along the neurovascular bundle in papillary dermis [Figure 2a]. Epidermis showed subcorneal collection of neutrophils [Figure 2b]. No acid-fast bacilli were seen on Wade-Fite staining.

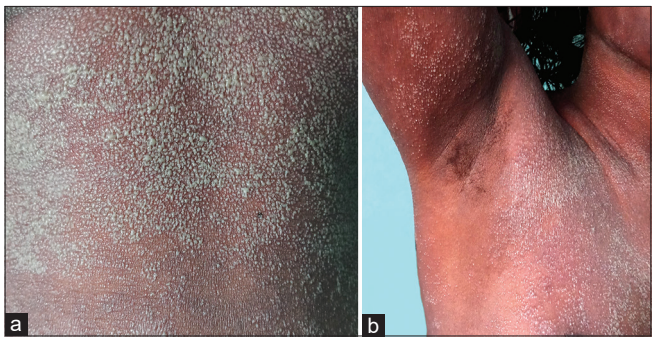

Figure 1(a): Numerous small pustules on the trunk of a patient who manifested minocycline-induced acute generalized exanthematous pustulosis; (b): Relative sparing of axilla in the same patient.

The score on Naranjo adverse drug reaction probability score was 9 (causality assessment – definite).[5] AGEP validation score [Table 1] was 9, indicating definite AGEP.[6]

We added clarithromycin (500 mg per orally once a day) to the treatment regimen instead of minocycline. After completing 6 months treatment with three drugs {clofazimine, ofloxacin, and minocycline (first 4.5 months)/ clarithromycin (subsequent 1.5 months)}, the treatment was continued with clofazimine (clofazimine was gradually tapered to 50 mg over a period of 10 months) and ofloxacin for 18 months. The patient completed the recommended duration of treatment without any further adverse events.

DISCUSSION

AGEP is considered as a severe cutaneous adverse reaction.[7] Pichler classified AGEP as a Type IVd delayed, T-cell-mediated hypersensitivity reaction.[8] In majority of cases (90%), AGEP is precipitated by drugs. Rarely, pathogens such as *Mycoplasma pneumoniae* can precipitate the reaction.[7] The most common drugs associated with AGEP are aminopenicillins, pristinamycin, quinolones, chloroquine, sulfonamides, terbinafine, and diltiazem.[7,9] There are a few reports of minocycline-induced AGEP in literature.[10]

Short latent period between the onset of drug intake and the appearance of symptoms is typical of AGEP.[7] However, in our case, the symptoms appeared 135 days after the initiation of the drug, which was unusual. It remains unclear, whether the anti-inflammatory effect of co-administered clofazimine has caused the delay in manifestation of AGEP in our patient. Lee *et al.* have described a patient who developed AGEP following phenytoin. The rash manifested after a latent period of 81 days and progressed to exfoliative dermatitis with eosinophilia, renal involvement, and raised liver transaminases.[11] The authors concluded that AGEP progressed to drug reaction with eosinophilia and systemic symptoms. This was unlikely in our case, since the patient did not develop eosinophilia or internal organ involvement and responded to withdrawal of the offender and antihistamine. Another less common finding noted by us was the relative sparing of axillae and cubital fossa, which are the commonly affected sites in classical AGEP.[7]

In our patient, skin biopsy was taken from a pustule on the abdomen. There were no clinically evident skin lesions of leprosy at the biopsied site, either at the time of biopsy or at any time during the course of the disease, but interestingly, there were histopathological features of borderline tuberculoid leprosy along with the features of AGEP. El-Darouti *et al.*, in their study on histopathology

Table 1: Acute generalized exanthematous pustulosis validation score (by EuroSCAR study group) in a patient who manifested generalized pustular rash following minocycline.

Feature	Points assigned by the diagnostic score	Points assigned to the patient who manifested pustular rash following minocycline
Pustules	Typical +2, compatible with the disease +1, and insufficient 0	2
Erythema	Typical +2, compatible with the disease +1, and insufficient 0	2
Distribution	Typical +2, compatible with the disease +1, and insufficient 0	1
Mucous membrane involvement	Yes, reduce 2 points No 0	0
Acute onset	Yes 0 No, reduce 2 points	0
Resolution within 15 days	Yes 0 No, reduce 2 points	0
Fever >38°C	Yes +1 No 0	1
Polymorphonuclear leukocytes >7000 cells/mmo^3	Yes +1 No 0	1
Histopathology		
Other diseases	-10	
Not representative	0	
Exocytosis of polymorphonuclear leukocytes	+1	
Subcorneal or intraepidermal non-spongiform or not otherwise specified pustules with or without papillary edema	+2	2
Spongiform subcorneal and/or intraepidermal pustules with papillary edema	+3	
Total score of the current patient		9

Scores 1–4: Possible; 5–7: Probable; 8–12: Definite

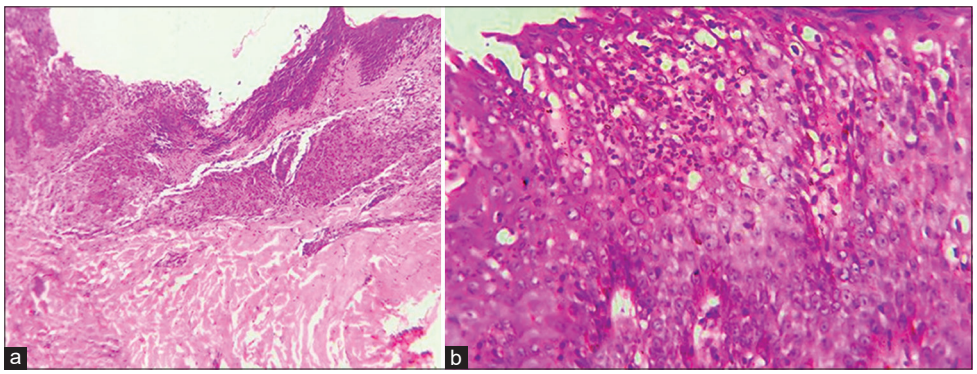

Figure 2(a): Skin biopsy of a pustule showing well-formed, epithelioid cell granulomas in a patient with leprosy who manifested minocycline-induced acute generalized exanthematous pustulosis (H and E, ×100); (b): high-power view showing collection of neutrophils in the stratum corneum with mild spongiosis (H and E, ×400).

of normal skin of leprosy patients, noted features of the disease in apparently normal looking skin in more than half of their cases (26 cases, 52%).[11] The normal looking skin of some of the lepromatous leprosy patients, in their study, showed borderline tuberculoid histopathology, which was comparable to our observation.[11]

The possibility of pustular ENL was ruled out in our case by the presence of epithelioid granuloma in lesional biopsy (neutrophil infiltration or neutrophilic vasculitis in the background of a macrophage granuloma is described as the histopathology feature in ENL), resolution of rash on withdrawal of the anti-leprosy drugs, and reappearance of

the same on rechallenge with minocycline.[12] Moreover, we noted collection of neutrophils in the subcorneal layer of epidermis rather than in the granuloma.

CONCLUSION

We report this case for the rarity of minocycline induced AGEP in a patient with lepromatous leprosy and recurrent ENL. Histopathology analysis and a drug re-challenge helped us to rule out pustular ENL.

Acknowledgment

We express our sincere gratitude to the faculty and residents of the departments of dermatology and pathology for their invaluable help. We thank Mr. Ashokan Rachana for helping us with the photographs.

Declaration of patient consent

Not required as patient's identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Mary Vineetha is on the editorial board of the Journal.

REFERENCES

1. Nadeem A, Jishna P, Sasidharanpillai S, Bindu V, Vidya A, Rahima S. Type 2 lepra reaction presenting as nasal septal perforation: A case report. J Skin Sex Transm Dis 2020;2:137-9.
2. Rahman N, Asokan N, Ambooken B. Leprosy presenting as eczema. J Skin Sex Transm Dis 2021;3:202-3.
3. Sirka CS, Rout AN, Purkait S. Recurrent pustular erythema nodosum leprosum: a rare case report. Indian Dermatol Online J 2021;12:439-40.
4. World Health Organization. Guidelines for the Diagnosis, Treatment and Prevention of Leprosy, Licence: CC BY-NC-SA 3.0 IGO. New Delhi: World Health Organization, Regional Office for South-East Asia; 2017.
5. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
6. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)—a clinical reaction pattern. J Cutan Pathol 2001;28:113-9.
7. Walsh S, Lee HY, Creamer D. Severe cutaneous adverse reactions to drugs. In: Barker J, Griffiths C, Bleiker T, Chalmers R, editors. Rook's Textbook of Dermatology. 9th ed. Wiley-Blackwell; 2016. p. 119.1-23.
8. Pichler WJ. Drug hypersensitivity reactions: Classification and relationship to T-cell activation. In: Pichler WJ, editor. Drug Hypersensitivity. Basel: Karger; 2007. p. 168-89.
9. Lee HY, Chou D, Pang SM, Thirumoorthy T. Acute generalized exanthematous pustulosis: Analysis of cases managed in a tertiary hospital in Singapore. Int J Dermatol 2010;49:507-12.
10. Yamamoto T, Minatohara K. Minocycline-induced acute generalized exanthematous pustulosis in a patient with generalized pustular psoriasis showing elevated level of sELAM-1. Acta Derm Venereol 1997;77:168-9.
11. El-Darouti MA, Hussein S, Marzouk SA, Nabil N, Hunter NS, Mahgoub D, *et al*. Histopathological study of apparently normal skin of patients with leprosy. Int J Dermatol 2006;45:292-6.
12. Sasidharanpillai S, Govindan A. Jopling's handbook of leprosy. In: Jopling's Handbook of Leprosy. Sardana K, Khurana A, editors. 6th ed. New Delhi: CBS Publishers; 2020. p. 116-46.

How to cite this article: Narayanan NK, Vineetha M, Palakkal S, Jayalakshmi PL, Skaria L, Issac CM, *et al*. Minocycline-induced acute generalized exanthematous pustulosis in a patient with lepromatous leprosy. J Skin Sex Transm Dis 2022;4:246-9.