Case Report

Combination of Low-Dose Methotrexate with Cyclosporine as Management for Generalized Pustular Psoriasis

Muhlis Muhlis[1], Widya Widita[2], Siti Nur Rahma[3], Wiwiek Habar[4], Thomas Utomo[5]

Abstract

Generalized pustular psoriasis (GPP) is a rare, life-threatening dermatosis marked by sterile pustules, systemic inflammation, and multi-organ involvement. We report a 26-year-old obese female with sudden-onset erythematous plaques, pustules, and erosions covering >90% of her body, accompanied by fever and arthralgia. Histopathology revealed Kogoj pustules and neutrophilic infiltrates, confirming GPP. Initial methylprednisolone therapy failed to prevent recurrence. Combination therapy with low-dose methotrexate (7.5–15 mg/week) and cyclosporine was initiated, alongside topical corticosteroids and wet dressings. Notable clinical improvement was seen within 30 days without any negative effects. This case highlights the synergistic effectiveness of methotrexate-cyclosporine treatment in refractory GPP cases, considering hyperproliferation is managed with methotrexate and T-cell activation is managed with cyclosporine. The response was quick, along with a good safety profile suggesting the treatment may be used instead of biologics where resources are limited. More research needs to be done to develop combination therapy protocols for GPP.

Keywords: Generalized pustular psoriasis, methotrexate, cyclosporine, combination therapy.

Received: 25-04-2024 **Revision:** 15-11-2024 **Accepted:** 19-02-2025

Authors Affiliation:
[1]Dermatology Venereology and Aesthetic Department, Bhayangkara Hospital, Makassar, South Sulawesi, Indonesia; [2]Dermatology Venereology and Aesthetic Department ,Hasanuddin Teaching Hospital, Makassar, South Sulawesi, Indonesia; [3,5]Dermatology, Venereology and Aesthetic Department, Faculty of Medicine, Hasanuddin University; [4]Dermatology Venereology and Aesthetic Department Akademis Jaury Jusuf Putera Hospital, Makassar, South Sulawesi, Indonesia
Corresponding Author: Muhlis Muhlis, Department Dermatology & Venereology Hasanuddin University, Perintis Kemerdekaan KM 11, Makassar, South Sulawesi, 90245, Indonesia. **Email:** docmuldv@gmail.com

Introduction

Generalized Pustular Psoriasis (GPP) is the rarest type of psoriasis. Leopold von Zumbusch was the first to describe pustular psoriasis in 1910.[1] It manifests with shallow non-infectious pustules about 2 – 3 mm in size which may be scattered or confluent over a red base.[1] Often painful and discomforting, these pus-filled bumps. GPP can occur with or without a prior history of plaque psoriasis and upon resolution it may involve other organs like skin causing arthritis, uveitis, and neutrophilic cholangitis. There is also a possibility of secondary sepsis due to bacterial infections which can be very dangerous.[1,2]

Generally, the management of GPP tries to incorporate supportive therapy focusing on topical management along systemics as well as identifying predisposing factors that lead to exacerbations of GPP. Some examples of these systemic therapy options for GPP are acitretin, cyclosporine, methotrexate (MTX), corticosteroids, and advanced biologic therapies like anti-TNF, IL-17 blockers and others.[1,3,4]

For those who experience severe but treatment-resistant GPP flares despite solo therapy approaches often resorting to step-up combination strategies for more rapid results. Using multiple therapies at once can improve effectiveness and decrease medication side effects.[3] Some studies and case reports have documented positive results with low side effects using a combination of methotrexate (MTX) and cyclosporine.[3] This case report involves a twenty-six-year-old female

patient with generalized pustular psoriasis treated with combination therapy of methotrexate and cyclosporine who achieved excellent outcomes without noted adverse effects.

Case Report

A 26-year-old female came to the Emergency Department complaining of red scaly patches and pus-filled bumps all over her body that had worsened over the past two days. She noticed a burning sensation along with itchiness. The lesions first developed on her back two weeks earlier as red patches which were itchy, but then progressed to more bump-like structures. The patient used salicylic powder but the lesions worsened over time and the bumps turned into pus. The patient also experienced joint pain, intermittent fever, and malaise. There was no consumption of any medications prior to these symptoms' appearance.

The patient was given methylprednisolone and paracetamol therapy one week prior. The lesions initially improved but soon recurred and increased in number. The patient never had a history of similar condition. The patient admitted to experiencing heavy psychological stress.

On physical examination, vital signs were within normal range. The patient's BMI was 29.2 kg/m2. Dermatological examination revealed erythematous scaly plaques with multiple pustules on top, erosions almost all over the body (Figure 1). Dermoscopic examination showed white scales, evenly distributed red dots, and pustules (Figure 2).

Gram staining of the pustules did not show presence of bacteria but there was a finding of scant neutrophilic inflammatory cells (Figure 3). Liver and kidney function tests were within normal limits. The patient underwent a histopathological examination which revealed features consistent with psoriasis-like rete ridges, hyperkeratosis (parakeratosis), hypogranulosis, dilatation of blood vessels in the dermal papillae, and the presence of Kogoj pustules in the epidermis. These histopathological findings supported the diagnosis of pustular psoriasis (Figure 3). The patient was then diagnosed as a suspected case of generalized pustular psoriasis (GPP) with a differential diagnosis of acute generalized exanthematous pustulosis (AGEP).

The patient was then treated with Methotrexate 7.5 mg/week orally, Cetirizine 10 mg/24 hours orally, Folic Acid 1000 mcg/24 hours orally. Topical treatments included two medications with the first one being a combination of Salicylic Acid 3% + Desoximethasone cream 30g + Vaseline album 50g given twice a day for lesions on the body, and the second medication being a combination of Hydrocortisone cream 2.5% + Gentamicin ointment 2% given twice daily. Erosions were compressed with wet gauze and irrigated with 0.9% NaCl.

On the third day of observation, new lesions still appeared, with most pustules turning into erosions. Fever was intermittent. Dermatological examination revealed erythematous plaques, scales, pustules, erosions, and hyperpigmented plaques almost all over the body (Figure 4). The patient was given additional therapy of Erythromycin 500 mg every 8 hours orally. On the fifth day of observation, new lesions were still appearing but the patient discharged herself from the hospital. Methotrexate dose was increased to 15mg/week orally, while other therapies were continued.

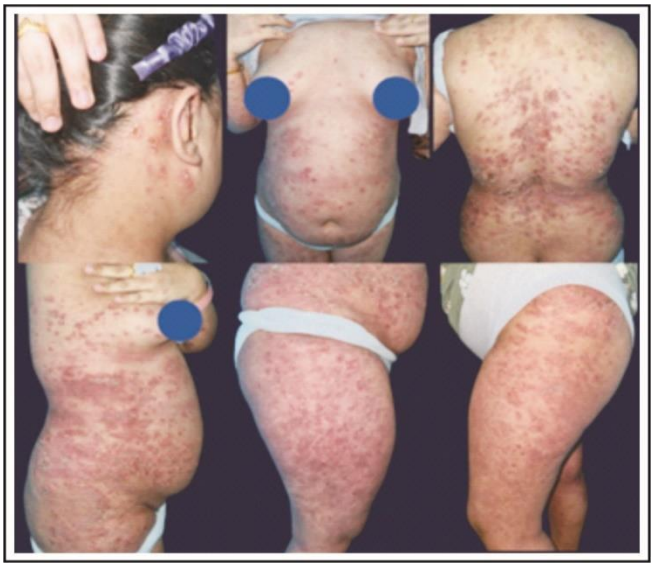
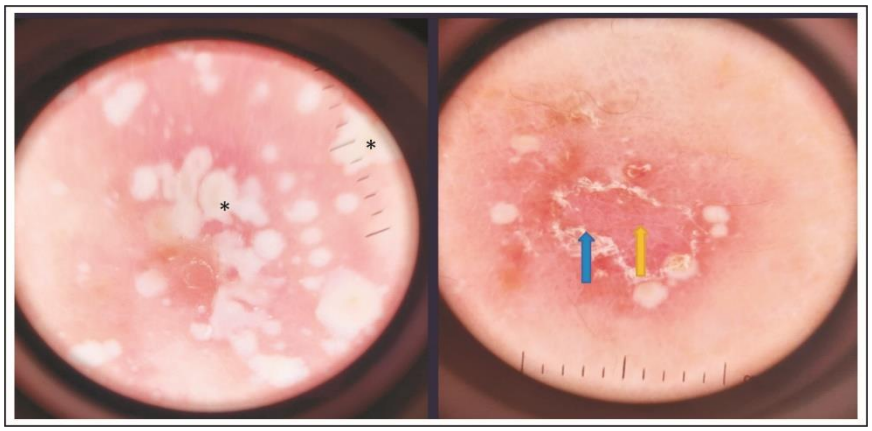


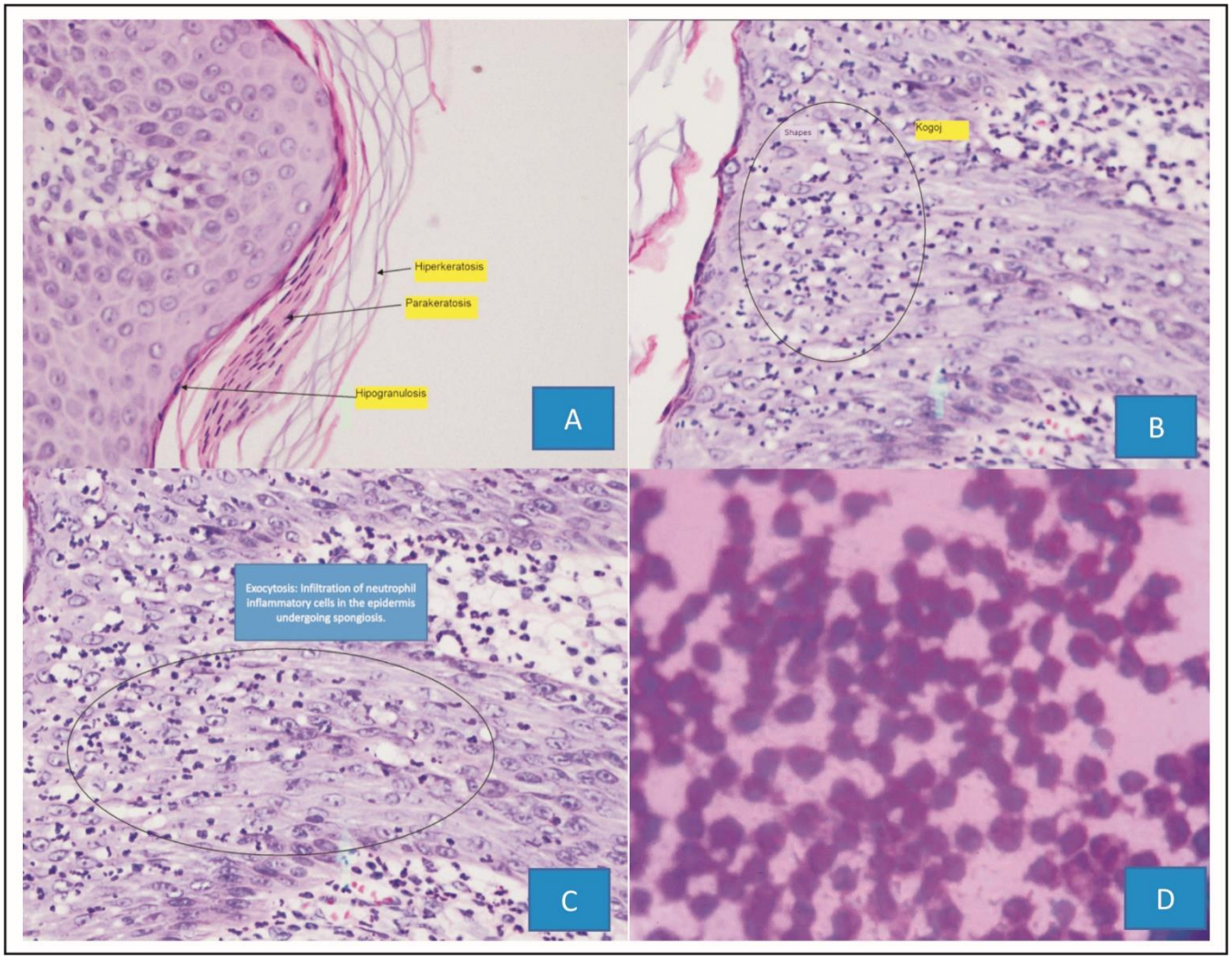
Figure 1: Generalized Pustular Psoriasis.

Discussion

A 26 – year – old female patient complained of red scaly patches accompanied by pus-filled bumps all over the body for the past 2 weeks. There was no history of previous medication intake prior to the lesion eruption. Intermittent fever and joint pain were experienced by the patient. The patient was then given oral methylprednisolone, which resulted in improvement of lesion but recurred and worsened

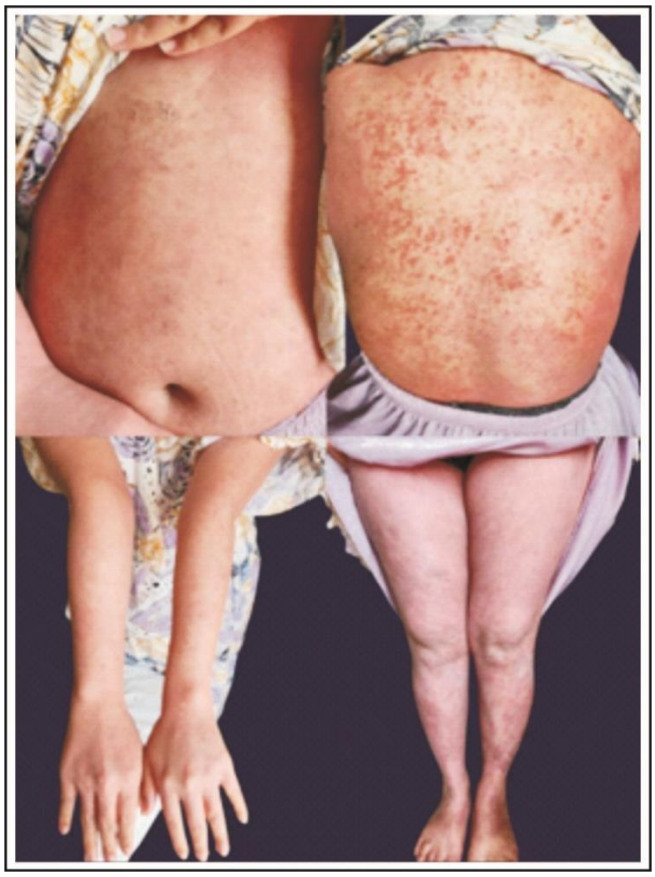


Figures 2: Dermoscopy: White scales (blue arrow), Red dots in an organized pattern (yellow arrow), pustules with a lack of pus appearance (*)



Figures 3A-C: Histopathological findings consistent with the diagnosis of Pustular Psoriasis, **3D:** Gram stain examination revealed neutrophil inflammatory cells, without the presence of bacteria (Sterile).

upon discontinuation. On physical examination, the patients BMI was within the range of obesity. Dermatological examination revealed generalized erythematous scaly plaques with multiple merging pustules (lake of pus). Gram staining of the pustules showed neutrophilic inflammatory cells without presence of bacteria. Routine blood tests showed increased leukocyte.



Figures 4: Day 30 Follow-up: Clinical improvement observed on the skin.

Generalized pustular psoriasis can occur at various ages, although it usually occurs during the fourth decade of life.1 The average age of onset of generalized pustular psoriasis (GPP) is 40.9 years, and there is no significant difference in onset based on whether individuals have a history of previous plaque psoriasis or not. Two previous studies found a higher prevalence of acute GPP in men, with rates ranging from 57% to 62%.[7] However, most studies indicate that the incidence of this disease is higher in women, with rates ranging from 53% to 63%.[5-6]

The underlying cause of GPP is not fully understood, but there is evidence suggests that GPP is a multifactorial disease caused by a combination of genetic, immunological, and environmental factors.[1] GPP is considered a systemic disease as it affects various organs including the liver, kidneys, heart, and lungs.[7] GPP can occur with or without previous plaque psoriasis, and the most common associated comorbidities include arthritis, uveitis, and neutrophilic cholangitis.[1] Additionally, the presence of sepsis caused by secondary bacterial infections can lead to severe consequences.[1,7,8]

Management of GPP generally involves supportive therapy, topical therapy, systemic therapy, and identification of triggering factors that may induce GPP.[1,2,9] Several systemic therapy options are available for GPP, including acitretin, cyclosporine, methotrexate, corticosteroids, and advanced biological therapies such as anti-TNF, anti-IL-17, anti-IL-36, and others.[1,3,4]

Cyclosporine is one of the most effective and rapid-acting drugs for the treatment of GPP, with a response rate of up to 80-90%.[1,10] However, long-term use of cyclosporine is associated with several adverse effects, including nephrotoxicity, hypertension, hyperlipidemia, gingival hyperplasia, hirsutism, and increased risk of infections and malignancies.[1,11] Methotrexate is another effective drug for the treatment of GPP, with a response rate of up to 80-90%.[1,12] Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase and reduces DNA synthesis and cell proliferation.[1,12] However, long-term use of methotrexate is associated with several adverse effects, including hepatotoxicity, bone marrow suppression, mucositis, and pneumonitis.[1,12]

Several studies and case reports have shown favorable outcomes and minimal side effects when using a combination of methotrexate and cyclosporine.[3,5] However, there is still limited evidence on the efficacy and safety of combination therapy compared to monotherapy.[3,5] A systematic review of the literature found only six studies evaluating the efficacy and safety of combination therapy for the treatment of GPP, with a total

of 28 patients.[3] Four studies reported favorable outcomes with no serious adverse events, while two studies reported serious adverse events requiring discontinuation of treatment.[3]

Conclusion

Combination therapy should be considered in patients with severe GPP who do not respond adequately to monotherapy or who experience intolerable adverse effects from the consumption of each drugs alone.[3,5] Combination therapy can enhance efficacy and reduce medication side effects by targeting different pathways involved in the pathogenesis of GPP.[3,5] However, further research is needed to better understand the efficacy and safety of combination therapy compared to monotherapy.[3,5]

Acknowledgment

The authors thank the dermatology team at Bhayangkara Hospital Makassar for their clinical support and the patient for consenting to this publication.

Disclaimer: The views expressed in this article are solely those of the authors and do not represent the official position of their affiliated institutions.

Conflict of Interest: There was no conflict of interest to be declared by any authors.

Funding Source: None.

Author's Contribution

MM: Conceived, designed, edited the manuscript, given final approval of the version to be published, critical revisions.

WW: Manuscript writing, final approval of the version to be published, agree to be accountable for all aspect of the work.

SNR: Manuscript writing, final approval of the version to be published, agree to be accountable for all aspect of the work.

WDH: Manuscript writing, final approval of the version to be published.

TU: Conceived, designed, edited the manuscript, given final approval of the version to be published, critical revisions.

References

1. Gudjonsson JE, Elder JT. Psoriasis. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al, editors. Fitzpatrick's Dermatology. 9th ed. New York, NY: McGraw-Hill Education; 2019 [Internet]. Available from: https://accessmedicine.mhmedical.com/content.aspx?aid=1161323116
2. Fujita H, Gooderham M, Romiti R. Diagnosis of generalized pustular psoriasis. Am J Clin Dermatol. 2022;23(Suppl 1):31-8.
3. Suwarsa O, Nursjamsi NCD, Pangastuti M, Sutedja E, Dharmadji HP. Keberhasilan terapi kombinasi menggunakan metotreksat injeksi dan siklosporin pada psoriasis pustulosa generalisata. Maj Kedokt Bandung. 2017;49(3):208-12.
4. Mirza HA, Badri T, Kwan E. Generalized pustular psoriasis. Treasure Island (FL): StatPearls Publishing; 2023.
5. Marrakchi S, Puig L. Pathophysiology of generalized pustular psoriasis. Am J Clin Dermatol. 2022; 23(Suppl 1):13-9.
6. Santoso FL, Budhiani S, Ilyas F. Profil psoriasis di Rumah Sakit RSWS, RSUP Hasanuddin, BP Kulit, Kelamin, dan Kosmetika periode Juli 2019-Juni 2023. Makassar; 2023.
7. Ly K, Beck KM, Smith MP, Thibodeaux Q, Bhutani T. Diagnosis and screening of patients with generalized pustular psoriasis. Psoriasis (Auckl). 2019; 9:37-42.
8. Wu Y, Sun L. Clinical value of dermoscopy in psoriasis. J Cosmet Dermatol. 2023 Sep 14 [Epub ahead of print].
9. Golińska J, Sar-Pomian M, Rudnicka L. Dermoscopic features of psoriasis of the skin, scalp and nails: a systematic review. J Eur Acad Dermatol Venereol. 2019;33(4):648-60.
10. Isom J, Braswell DS, Siroy A, Auerbach J, Motaparthi K. Clinical and histopathologic features differentiating acute generalized exanthematous pustulosis and pustular psoriasis: a retrospective series. J Am Acad Dermatol. 2020;83(1):265-7.
11. Hsieh TS, Tsai TF. Combination therapy for psoriasis with methotrexate and other oral disease-modifying antirheumatic drugs: a systematic review. Dermatol Ther (Heidelb). 2023;13(4):891-909.
12. Angelina C, Tan ST. Perubahan kualitas hidup DLQI sebelum dan sesudah penggunaan krim racikan anti jerawat klinik Sukma. J Suplemen [Internet]. 2023 [cited 2023 Dec 6];15. Available from: https://lintar.untar.ac.id/repository/penelitian/buktipenelitian_10413003_4A070723140148.pdf