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Combination of Low-Dose Methotrexate and Cyclosporine in a Patient with Generalized Pustular Psoriasis: A Case Report

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ABSTRACT
Generalized pustular psoriasis (GPP) is a rare and life-threatening chronic inflammatory skin disease characterized by sterile pustules and systemic inflammation, associated with substantial disease burden due to frequent flares. Limited guidelines and suboptimal treatment outcomes have led to various therapeutic approaches, including combination therapy. This case report aims to describe the use of low-dose methotrexate and cyclosporine combination in a GPP patient and evaluate the clinical response achieved. A 40-year-old woman presented with painful pustules distributed throughout the entire body accompanied by a burning sensation. She had undergone methotrexate therapy for 1 year before self-cessation due to insignificant improvement. Dermatological examination revealed generalized multiple pustules on an erythematous base, some confluent and covered by scales. Histopathological examination showed abundant neutrophils in the superficial epidermal layer along with focal neutrophils and mild spongiosis, supporting the diagnosis of GPP. The patient was given methotrexate 7.5 mg weekly and cyclosporine 100 mg daily for 5 weeks, showing significant clinical improvement, then maintained with methotrexate 7.5 mg weekly monotherapy. Combination therapy for GPP, particularly methotrexate and cyclosporine, has demonstrated faster and better clinical responses compared to monotherapy, with response rates of 70–90%. Cyclosporine provides rapid disease control, while methotrexate offers sustained immunomodulation. Both agents carry risks of adverse effects, necessitating careful dose selection and close monitoring. This case report demonstrates that low-dose methotrexate and cyclosporine combination is effective in managing refractory GPP with significant clinical improvement after 5 weeks of therapy, making it a promising therapeutic option for severe and refractory GPP cases.

INTRODUCTION

Psoriasis is characterized by scaly erythematous patches or plaques that commonly occur on extensor surfaces but may also affect intertriginous areas, the palms, soles, and nails. Psoriasis affects males and females with similar frequency and is more prevalent among adults than children (Kevat et al., 2025). A combination of genetic predisposition and environmental factors contributes to the development of psoriasis. Various triggers, including stress, infections, and medications, may precipitate disease onset or exacerbation. Individuals with a

family history of psoriasis have a higher risk of developing the condition (R SCM et al., 2025). Conventional therapies for psoriasis include topical treatments, phototherapy, and systemic medications. Topical corticosteroids, vitamin D analogs, and calcineurin inhibitors are commonly used as first-line therapies for mild to moderate disease. Phototherapy options include narrowband ultraviolet B (NB-UVB) and psoralen plus ultraviolet A (PUVA), which provide effective disease management with relatively few adverse effects. Systemic therapies, including methotrexate (MTX), cyclosporine, and acitretin, are indicated for moderate to severe cases that are refractory to topical therapy or phototherapy (Hung & Lamichhane-khadka, 2026; Singh, 2024).

Generalized pustular psoriasis (GPP) is a rare and severe chronic inflammatory skin disease characterized by the sudden onset of sterile pustules, often accompanied by systemic inflammation. GPP recurrence can be life-threatening if left untreated due to the potential development of serious complications, including sepsis and cardiovascular disorders. GPP is classified into several clinical subtypes based on disease onset, recurrence patterns, and lesion morphology (Zhao & Li, 2020). The von Zumbusch type represents the most severe and potentially life-threatening form, characterized by rapid onset within ≤7 days and generalized pustular eruptions, occurring in up to 90% of GPP patients. Lapière–Millian type is characterized by circinate or annular lesions with peripheral pustules, developing within 7 days to 3 months and generally accompanied by relatively mild systemic symptoms. Pustular lesions that initially appear in acral areas and gradually spread to form generalized pustular eruptions are classified as acral GPP. Mixed GPP types demonstrate characteristics of more than one subtype simultaneously (Poplausky, 2023). Differential diagnoses of GPP include acute generalized exanthematous pustulosis (AGEP) and subcorneal pustular dermatosis (SPD). In AGEP, clinical examination typically reveals small, nonfollicular pustules with acute onset following drug exposure and widespread distribution, while histopathological findings demonstrate subcorneal or intraepidermal pustules, spongiosis, and eosinophilic infiltration. In contrast, GPP exhibits psoriasiform epidermal hyperplasia and Kogoj spongiform pustules without predominant eosinophilic infiltration. SPD represents another differential diagnosis, characterized clinically by symmetrical flaccid pustules on the trunk and flexural areas, with histopathology showing subcorneal pustules containing neutrophils without psoriasiform epidermal changes. This differs from GPP, which demonstrates characteristic psoriatic epidermal alterations and more diffuse inflammatory infiltration (Bhargva, 2020; Stadler & Oschmann, 2023).

The management objectives of GPP can be divided into short-term and long-term goals. Immediate therapeutic goals during acute flares include improving skin manifestations and reducing systemic symptoms, whereas long-term goals focus on preventing recurrence and disease progression. Nonbiologic systemic therapies, including corticosteroids, acitretin, cyclosporine, and MTX, may be used as first-line treatment options. Other therapeutic agents with limited evidence include mycophenolate mofetil, hydroxyurea, apremilast, and colchicine. Cyclosporine is frequently preferred due to its rapid onset of action, particularly in acute and potentially life-threatening GPP flares (Elewski & Lebwohl, 2025).

In patients experiencing severe GPP flares that are resistant to single-agent therapy, combination treatment strategies may be considered to achieve faster clinical responses. Several studies and case reports have reported favorable outcomes with minimal adverse

effects using a combination of MTX and cyclosporine. Cyclosporine is considered one of the most effective and rapidly acting treatments for GPP, with reported response rates of 80–90%. Methotrexate is also an effective folate antagonist for GPP management, with reported response rates of up to 80–90%. Its mechanism of action involves inhibition of dihydrofolate reductase, resulting in reduced deoxyribonucleic acid (DNA) synthesis and cellular proliferation (Fujita et al., 2022). The management of GPP remains challenging due to its variable clinical course, risk of severe complications, and limited evidence regarding optimal therapeutic strategies (Puig et al., 2024).

This report aims to describe the use of combination therapy with methotrexate 7.5 mg weekly and cyclosporine 100 mg daily in a patient with severe GPP flare, while highlighting clinical considerations in treatment selection to achieve rapid and effective disease control with minimal risk of adverse effects. Theoretically, this report contributes to the limited literature regarding combination therapy for GPP and enhances understanding of therapeutic strategies for this rare and potentially life-threatening condition. Practically, it provides clinical insights for dermatologists managing GPP refractory to monotherapy by offering guidance on dose selection, combination strategies, and monitoring protocols, while also serving as a reference for future research on evidence-based therapeutic approaches for severe inflammatory skin diseases.

METHOD

This study employed a case report method to systematically describe the clinical characteristics, management, and outcomes of a patient. A 40-year-old woman presented with a complaint of recurrent purulent lesions distributed throughout the body, which had first appeared approximately 20 years earlier. Initially, the pustular lesions developed on the hands and feet before gradually spreading to other body areas. The symptoms were accompanied by itching, tenderness, pain, and a burning sensation. The patient had previously received treatment from a dermatologist and venereologist at a local general hospital (RSUD), including topical therapy and methotrexate (MTX) tablets at a dose of 10 mg weekly for one year, without significant clinical improvement. Therefore, the patient was referred to the Dermatology and Venereology Clinic of Dr. Moewardi Hospital for further evaluation and management. Dermatological examination revealed erythematous plaques with multiple discrete pustules in generalized areas, some of which were confluent and covered with scales (Figure 1).

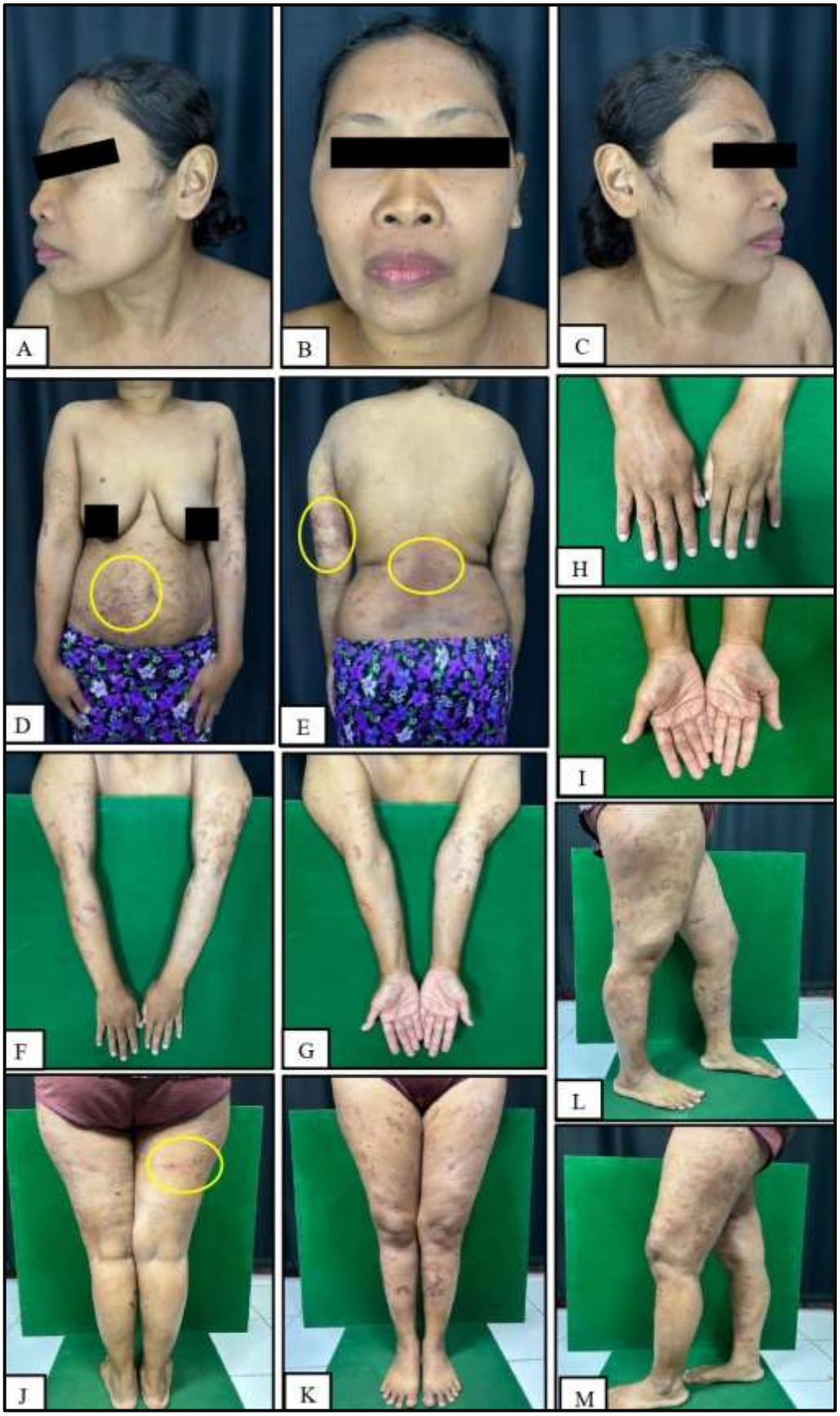

Figure 1. (A-M) In the generalized region erythematose plaques with discrete multiple pustules, some of them are confluent with squama on them. A picture of the lake of pustules

in the abdominal region, trunkus, antebrachii sinistra and posterior femoral dextras (yellow circles) is visible.

Source: Researcher's Documentation, 2026

The patient's previous treatment history included phototherapy at a dose of 600 mJ/cm², methotrexate (MTX) tablets 10 mg weekly, methylprednisolone tablets 8 mg daily, zinc tablets 20 mg daily, folic acid tablets 400 mcg daily, ranitidine tablets 150 mg every 12 hours, and topical therapy consisting of a mixture of deoxymethasone cream 0.25% and gentamicin cream 0.1% in a 1:1 ratio applied to erythematous areas twice daily. The patient had a history of acute generalized exanthematous pustulosis (AGEP) associated with metamizole and ibuprofen use. A family history of similar skin disorders, hypertension, diabetes mellitus, allergies, and other dermatological diseases was denied. The patient was a housewife and lived with her only child. She reported experiencing stress and difficulty sleeping at night due to concerns regarding her child's unemployment.

Histopathological examination of a skin biopsy revealed groups of neutrophils in the superficial epidermal layer, focal neutrophilic infiltration forming Kogoj spongiform pustules, and mild focal spongiosis (Figure 2), supporting the diagnosis of generalized pustular psoriasis (GPP). The patient was treated with methotrexate 7.5 mg weekly and cyclosporine 100 mg daily, along with folic acid 400 mcg daily, ranitidine 150 mg every 12 hours, sucralfate syrup 1 tablespoon every 8 hours, and topical therapy consisting of a mixture of clobetasol propionate cream 0.05% and Vaseline in a 1:1 ratio. Combination therapy with methotrexate 7.5 mg weekly and cyclosporine 100 mg daily resulted in significant clinical improvement after five weeks of treatment, followed by maintenance therapy with methotrexate 7.5 mg weekly monotherapy. The patient reported improvement in erythema and pustular lesions. Physical examination demonstrated marked improvement, with fading erythematous plaques and near-complete resolution of pustules after five weeks of therapy (Figure 3).

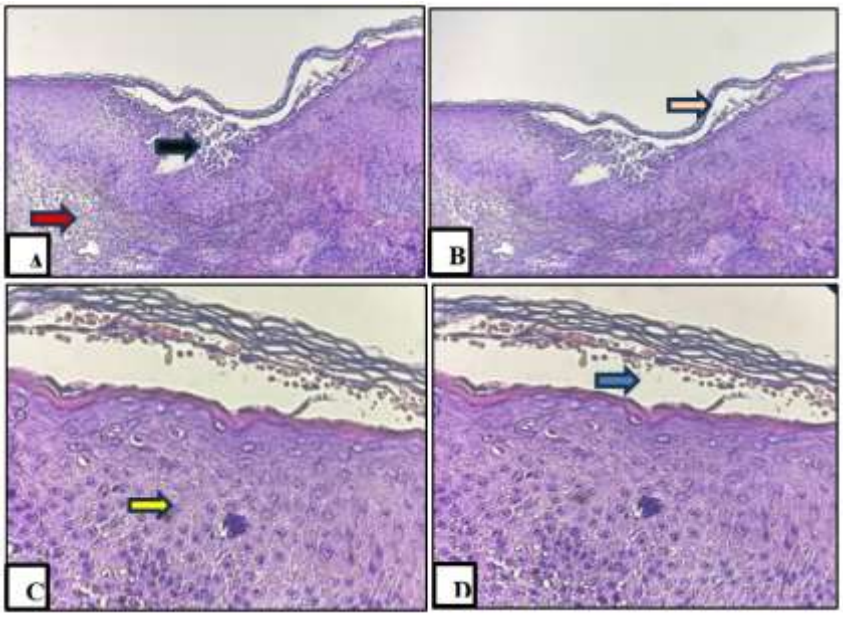

Figure 2. (A) In the layer inside the epidermis, a collection of neutrophil cells can be seen forming the Kogoj spongiform pustules (black arrows). In the dermis layer, a very minimal perivascular infiltrate is seen (red arrow). (B) In histopathology, an image of the superficial layer of the epidermis appears to be a group of neutrophil cells forming a Munro microabscess (green arrow). (C) Focal spongiosis appears and in mild degrees (yellow arrow). (D) A group of neutrophil cells under the stratum corneum (blue arrow)

Source: Researcher's Documentation, 2026

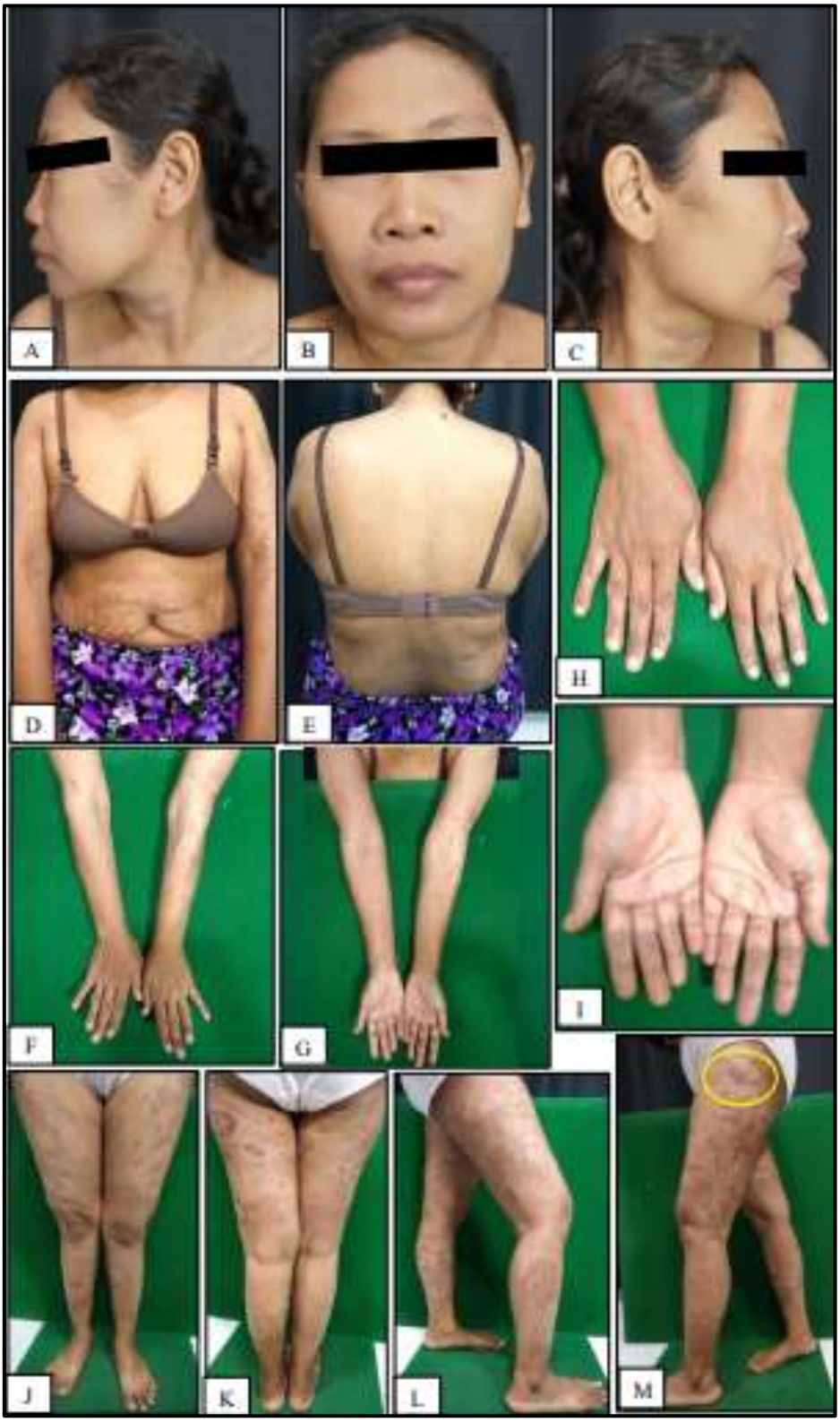

Figure 3. (A-M) The patient's condition after 5 weeks of treatment, in the generalisata region, erythematous plaques and pustules appear to be almost completely lost (M). In the lateral femoral region of sinistra, a picture of a lake of pustules (yellow circle) is seen.

Source: Researcher's Documentation, 2026

RESULT AND DISCUSSION

Psoriasis vulgaris is a chronic inflammatory skin disease that is generally characterized by pink plaques with firm borders and silvery scales that often affect the scalp, elbows, knees and presacral areas (Menter et al., 2020). The incidence rate of this disease in the general population varies with prevalence in East Asia being 1.58% (Parisi et al., 2020). The cause of psoriasis is still unknown but it is suspected that the lesions that appear are the result of hyperproliferation and differentiation of the epidermis abnormal. The main pathological process is thought to originate from the immune system, specifically the presence of abnormalities in the regulation of interleukin (IL)-2, growth factors or adhesion molecules (Camisa, 2020). The management of psoriasis is divided into several levels of therapy. Level 1 therapy in the form of topical treatment begins with the use of emollients followed by keratolytic lotions, topical corticosteroids and calcipotriene ointments or creams. Level 2 therapy is phototherapy, which is very effective (80–100%) in clearing lesions, but requires maintenance therapy. Level 3 therapy is a systemic treatment that is more effective than phototherapy. Level 4 and 5 therapy where level 4 therapy is mild to moderate effectiveness with lower toxicity while level 5 therapy is intended for the most severe and refractory cases, including those with arthropathy.

Pustulose psoriasis encompasses a spectrum of inflammatory skin conditions that are chronic, persistent to intermittent or recurrent, with a variety of different clinical phenotypes, including PPG, acrodermatitis continua of Hallopeau, PPG in pregnancy (impetigo herpetiformis), annular pustulose psoriasis and palmoplantar pustulosis (PPP) (Benezeder et al., 2025). Pustulose generalisata psoriasis is a rare and severe chronic inflammatory skin disease characterized by the sudden appearance of sterile pustules as well as often accompanied by a systemic inflammatory response (April, 2024; Daude & Puig, 2023). Gender dominance in PPG cases is female. Recent data from an inpatient database covering 1,516 PPG patients in Japan show that 56% of patients are male and a registry in western Japan also reported that 52% of the 102 PPG cases were male (Zheng et al., 2022). The majority of cases occur in the fifth decade of life with the average age at diagnosis ranging from 45.6–50.0 years. Other reports also mention that women tend to be diagnosed at a younger age (average of 39.4 years) than men. The main factor contributing to the high burden of disease is recurrent recurrence, which leads to hospitalization in about 50–90% of cases (Koivusalo et al., 2025). Relapse can be triggered by re-exposure to triggering factors or can occur without a known cause (Zafiriou et al., 2024). Certain triggering factors are known to trigger systemic corticosteroid rapid discontinuation, infection, pregnancy, menstruation and stress. Other potential triggers that have been identified include hypocalcemia and vaccination. Drug use has also been reported as a triggering factor (Table 1). This is consistent with findings in these patients who are now 40 years old with symptom onset at age 20. Potential triggers of this case are possible history of use and methylprednisolone and history of AGEP due to metamizole and ibuprofen according to theory.

Table 1. Triggering Factors of PPG

Category	Triggering factors
Medications	Systemic corticosteroids (discontinuation), vaccines including COVID-19 vaccines, betamethasone ointments, calcipotriol ointments, OAINS, progesterone, terbinafin, penicillin, lithium, iodine, amoxicillin, cyclosporine, hydroxychloroquine, anti-TNF use and other biologics

Comorbidities Infections Miscellaneous	*Streptococcus*, *trichophyton rubrum*, sitomegalovirus, virus *Epstein–Barr*, virus varisela zoster, infeksi COVID-19
	Hypoparathyroidism, hypocalcemia, pregnancy, menstruation, stress

Source: Daude & Puig (2023)

Coronavirus = COVID, nonsteroidal anti-inflammatory drugs = NSAIDs, tumor necrosis factor = TNF

Acute generalized exanthematous pustulosis is one of the differential diagnoses of generalized pustular psoriasis because it can cause diffuse pustules on erythematous skin. The clinical manifestation of AGEP is usually small, sterile, non-follicular pustules that initially appear on the face or intertriginosa area and then spread acutely within 24–48 hours after taking the triggering drug. The histopathology of AGEP generally shows subcorneal or intraepidermal pustules accompanied by spongiosis as well as superficial perivascular inflammatory infiltrates consisting of lymphocytes, neutrophils and eosinophils, with the contents of pustules dominated by neutrophils. The main differences with PPG are a clear history of drug origin, very fast onset and the presence of eosinophils and spongiosis in histopathology, while in PPG spongiform pustules are usually found Kogoj, psoriasiform epidermal hyperplasia and are generally not directly related to acute drug reactions. In patients there are similarities with AGEP in the form of diffuse pustules with the predominance of neutrophils in the epidermis and the presence of mild spongiosis. The distinguishing factor of AGEP is that in this patient there is no history of pustules appearing immediately after taking medications and no eosinophils are found in the skin histopathology.

Sneddon–Wilkinson syndrome, also known as pustular subcorneal dermatosis (DSP), is a differential diagnosis of PPG. On the physical examination of the DSP, it was found that sterile pustules were flaxed and symmetrically arranged, especially on the torso and flexural areas such as the armpits and folds of the extremities. The initial lesion can be a papule or a small vesicle that then develops into a pustule, with a typical hypopolar appearance (half-half appearance) where the lower part of the pustule contains pus and the upper part contains clear fluid. Pustular subcorneal dermatosis indicates a subcorneal pustule that contains mainly neutrophils with little or no spongiosis. The fundamental difference between DSP and PPG is that DSP does not have epidermal changes typical of psoriasis such as psoriasiform hyperplasia or Kogoj spongiform pustules and the distribution of lesions is more limited to extremities and flexors and is usually not accompanied by severe systemic inflammation as in PPG.8 In patients there are similarities with DSP in the form of diffuse pustules with the predominance of neutrophils in the epidermis and the presence of mild spongiosis. It is different from DSP in that the lesions in patients are widespread throughout the body and have been chronic for ±20 years whereas DSP is generally limited to the extremities and flexural areas.

The pathogenesis of PPG is dominated by the activation of the innate immune system and primary genetic factors that cause innate immune hyperactivation. At the molecular level, the cytokine pathways that are dominant in both diseases are also different, where plaque psoriasis is primarily mediated by the IL-23/IL-17 axis whereas growing evidence suggests that the IL-36 pathway plays a central role in the pathogenesis of PPG (Figure 4). The cytokine IL-36, which is part of the IL-1 family, is expressed by keratinocytes, epithelial cells and immune cells and acts autocrestically and paracrine to regulate the innate immune response.5 Dysregulation of IL-36 signaling through the IL-36 receptor complex and the IL-1R accessory

protein leads to a sustained inflammatory cascade in the epithelium. Overexpression of IL-36 agonists (IL-36α, β, or γ) or dysfunction of IL-36 receptor antagonists (IL-36RA) due to IL36RN gene mutations can trigger a positive feedback loop in the form of uncontrolled signal activation and overproduction of proinflammatory cytokines. This condition triggers the induction of chemokines such as chemokin ligands (CXCL)1 and CXCL8 to form a chemokine gradient that attracts large numbers of neutrophils to the epidermis resulting in the formation of Kogoj spongiform pustules and the accumulation of subcorneal neutrophils that appear as lakes of pustules, a typical PPG picture. The cytokine pathways IL-36 and IL-23 are known to interact closely with each other so that dysregulation of one of these pathways may maintain a chronic inflammatory response in PPG (Marrakchi & Puig, 2022).

Generalisata pustulosa psoriasis is characterized by the appearance of primary sterile pustules that appear macroscopically on non-acradial skin and are not limited to psoriasis plaques. Sterile pustules are considered primary lesions that after drying can form a squamic or brownish crust that then slowly peels off. The presence of the cyst can be evidence of pustules, especially in cases when fresh pustules are no longer found.10,16 In this case, similarities were found in the form of widespread pustules with complaints of pain, stinging and hot sensation (Table 2).

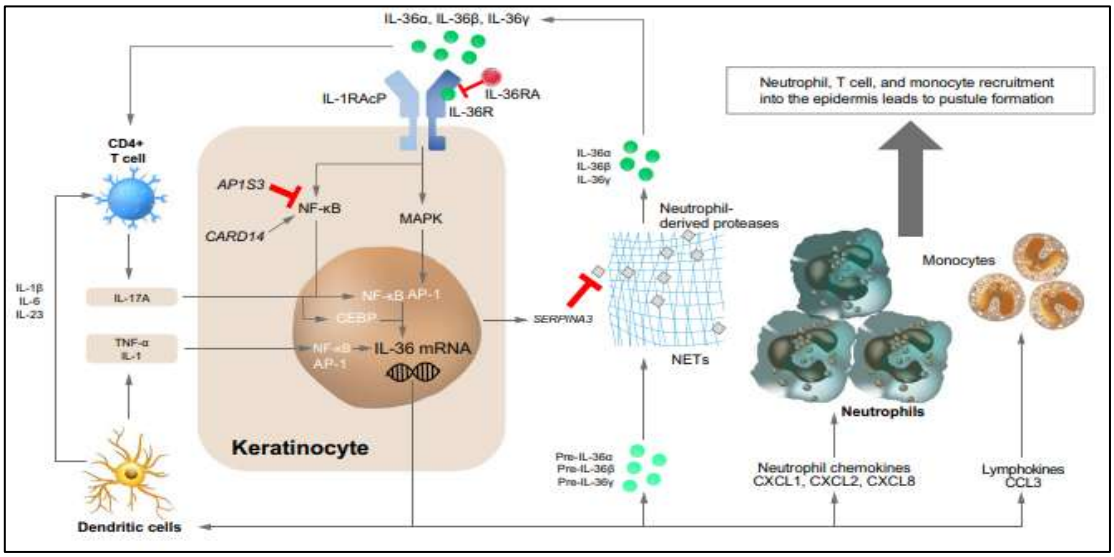

Figure 4. Pathophysiology of PPG
Source: Marrakchi & Puig (2022)

Table 2. Classification of PPG

Type	Clinical Picture	Subclassification
Generalized form		
Pustular generalisata	Primary, sterile, macroscopic appearance pustules on non-acral skin (excluding cases where pustula is limited to plaque psoriasis)	With or without systemic inflammation; with or without psoriasis vulgaris; single episode (≤1 *episode*) or persistent (>3 months)
Special shape PPG		
Impetigo Herpetiformis	Erythematous patches with sterile pustules clustered at the edges, especially in the third trimester of pregnancy; It mainly appears in the flexural region, then it can expand	—

	centrifugalously, develop into a crustacean, and can even be secondary infected (impetiginization)	
Psoriasis pustular annular	Erythematose plaques are squamatous with a firm boundary accompanied by central clearance	—
Localized form		
Acrodermatitis *continue of Hallopeau*	Primary, persistent pustules (>3 months), sterile, macroscopic appearance that hits the nail apparatus	With or without psoriasis vulgaris
Pustulosis palmoplantaris	Primary pustules, persistent (>3 months), sterile, macroscopic appearance on the palms and/or soles of the feet	With or without psoriasis vulgaris

Source: Marzano et al. (2025)

Psoriasis pustulosa generalisata = PPG

Pustulose generalisata psoriasis is further classified based on the presence or absence of comorbidity manifestations such as systemic inflammation, plaque psoriasis lesions and the course of the disease whether it is relapsed or persistent. Systemic inflammatory criteria include increased blood precipitation rate (LED) and c-reactive protein (CRP) as well as clinical signs of fever >38°C and leukocytosis with leukocyte count >12 × 10^9/L. Diagnosis of PPG is established when the disease has experienced at least one recurrence (relapse type) or shows persistent pustulatic.

A skin biopsy may be required in certain cases especially to distinguish PPG from AGEP. In PPG histopathological examination, epidermal hyperplasia with parakeratosis and acanthosis, elongation of rete ridges and thinning of the stratum granulosum layer can be found. In the dermis, there are inflammatory infiltrates dominated by neutrophils that migrate from the papillary capillaries to the epidermis and form a distinctive intraepidermal pustular infiltrate. In the histopathological examination of the patient's skin, a picture of neutrophil cell groups in the superficial epidermis appeared, intraepidermal focal neutrophil infiltration, mild spongiosis, minimal perivascular infiltrates and no eosinophils were found, thus ruling out the diagnosis of AGEP because in AGEP dermal eosinophils are generally found.

Assessment of disease severity requires a thorough clinical examination, an accurate anamnesis as well as laboratory examinations. Initial laboratory tests that need to be done include complete blood counts, CRP, urine analysis and blood protein electrophoresis. In patients with high fever and severe clinical conditions, blood cultures and comprehensive metabolic examinations are required to assess hypocalcemia, other electrolyte disorders, hypoalbuminemia and kidney and liver function (Marzano et al., 2025).

Therapies for PPG include a variety of therapies that were initially approved for other indications and then used for PPG and can generally be classified into three groups, namely biologic therapies, nonbiologic systemic therapies and other therapies (Table 3). Current PPG therapy has limitations, where the resolution of recurrence is often slow and the cleansing of pustules and skin lesions is not perfect (Gao et al., 2025). Supportive management includes hospital care which is an important part of PPG management. Improvements to PPG therapy, including the development of specific therapies, have the potential to reduce the need for such intensive care and reduce the burden on both the health system and patients (Chen et al., 2024; Henricks et al., 2026). The potentially life-threatening nature of PPG underlies the need for

therapies with rapid onset and a good safety profile to manage recurrence and lower the burden of disease.

PPG recurrences often persist even when given a single therapy, so a gradual combination approach is often used to obtain faster results. The use of several therapies simultaneously can increase the effectiveness and lower the side effects of the drug. Some studies and case reports show good results with minimal side effects through the combination of MTX and cyclosporine. Cyclosporine is one of the most effective and fast-acting drugs for PPG therapy with a response rate of up to 80–90%. Long-term use of cyclosporine is associated with a variety of side effects, such as nephrotoxicity, hypertension, hyperlipidemia, gingival hyperplasia, hirsutism as well as an increased risk of infection and malignancy (Febiyanto, 2021; Muhlis et al., 2025; Ozawa, 2025).

Table 3. Therapeutic options on PPG

Therapy biology	Nonbiological systemic therapies	Other therapies
TNF Inhibitors	**Corticosteroid**	**Phototherapy**
• Adalimumab	**Agen imunosupresan**	• PUVA
• Certolizumab pegol	• Hydroxyurea	**Apheresis**
• Etanercept	• Leflunomid	• GMA
• Infliximab	• Metotreksat	**Miscellaneous**
IL-17A Inhibitor	• Mikofenolat mofetil	• Colquisin
• Ixekizumab	• Siklosporin	• Glisirhizin
• Secukinumab	• Takrolimus	• Corticosteroid topical
Antagonis receptor IL-17	**Retinoid**	• Vitamin D
• Brodalumab	• Asitretin	• Zinc acetate
IL-12/23 Inhibitor	• Etretinat/Ro-10-9359	• Antibiotics
• Ustekinumab	• Isotretinoin	• Dapson
IL-1 inhibitors	**Fumarate**	• Tiamfenikol
• Anakinra	• Ester asam fumarat	
• Canakinumab	**PDE-4 Inhibitors**	
• Gevokizumab	• *Apremilast*	
IL-23 Inhibitors		
• Guselkumab		
• Risankizumab		
IL-36 Inhibitors		
• Imsidolimab		
• Spesolimab		
•Antibodi monoklonal anti-IL-36R		
Antibodi monoklonal anti-CD6		
• Itolizumab		

Source: Puig et al. (2024)

Interleukin = IL, Granulosit-monosit aferesis = GMA

Patients have previously received various therapy modalities according to the stages of psoriasis management, ranging from topical corticosteroids, phototherapy with a dose of 600 mJ/cm² to systemic therapy of MTX tablets 10 mg per week per week for one year without meaningful clinical improvement. This condition shows that the patient's disease is included in the severity and is refractory to conventional therapy.

Methotrexate is also an effective drug for PPG with a response rate of up to 80–90%. Methotrexate is a folic acid antagonist that inhibits dihydrofolate reductase, thereby lowering DNA synthesis and cell proliferation. Long-term use of MTX can cause side effects such as hepatotoxicity, bone marrow suppression, mucositis, and pneumonitis.27 Side effects can be reduced if combination therapy successfully lowers the dose of each drug compared to when used as monotherapy. A study by Singh, et al. (2021) explains that the weekly intramuscular MTX route is better used than the oral route which aims to ensure bioavailability, improve patient adherence, minimize gastrointestinal side effects as well as prevent accidental MTX overdose which is one of the most frequent causes of acute MTX toxicity (Singh, 2021).

Methotrexate and cyclosporine are two systemic agents traditionally used to treat moderate to severe psoriasis. Both were shown to be effective in treating severe psoriasis at a tertiary referral hospital in Indonesia with a significant reduction in PASI scores in patients receiving cyclosporine and MTX. Cyclosporine showed higher effectiveness, but the difference was not statistically significant. A meta-analysis study also found that cyclosporine was more effective than MTX in achieving PASI-75, although the difference was not statistically significant. A clinical trial by Heydendael in 2003 showed that administration of 15 mg MTX tablets per week and cyclosporine tablets 3 mg/kgBB/day for 16 weeks was able to lower PASI scores by up to 25% in 94% of patients (Umborowati et al., 2023). Another study explained that administration of cyclosporine tablets at a dose of 3–5 mg/kg/day and MTX tablets 10–15 mg per week resulted in clinical improvement in 7 patients after 6 months. These results showed that 70% of patients showed a good to very good response to the combination therapy and discontinuation of either drug led to a slowdown in the healing process (Aydin et al., 2016).

Patients were given combination therapy of MTX tablets 7.5 mg per week and cyclosporine tablets of 100 mg per day and showed clinically significant improvement after 5 weeks of drug use, followed by monotherapy in the form of MTX tablets 7.5 mg per week as maintenance therapy. Patients show clinically significant improvement characterized by fading erythematous plaques as well as almost total loss of pustules. This good clinical response is consistent with the theory that the combination of MTX and cyclosporine is effective in treating refractory PPG with a faster onset of work and more optimal clinical outcomes than monotherapy.

Combination therapy using cyclosporine and MTX is recommended as a good combination because it can minimize the laboratory side effects of cyclosporine and MTX in the treatment of psoriasis. Combination therapy approaches using cyclosporine and MTX can reduce the likelihood of developing nephrotoxicity. Combination therapy of MTX and cyclosporine showed a faster onset of action than MTX monotherapy and provided better outcomes in achieving psoriasis area and severity index (PASI) 75, PASI 90 and PASI 100 with side effects similar to MTX monotherapy (Tsai et al., 2023). The combination of cyclosporine and MTX can minimize side effects during systemic psoriasis therapy and may lower the dosage and side effects of each agent. This allows for better disease control with lower toxicity. The combination of MTX and cyclosporine is also effective in cases of recalcitrant PPG. The combination of MTX tablets of 7.5–15 mg per week with cyclosporine tablets of 3 mg/kgBB/day was reported to provide better improvement of psoriasis lesions as well as fewer side effects compared to monotherapy of the respective agents. A case study of severe psoriasis reported clinically significant improvement after combination therapy of 10

mg intramuscular MTX tablets per week and 3.5 mg/kgBB/day cyclosporine tablets for a median of 9.5 weeks with mild and easy-to-manage short-term side effects (Suwarsa et al., 2022).

This combination therapy has been shown to increase efficacy and reduce side effects in the management of moderate-to-severe psoriasis. Mohanan, et al. (2023), a prospective study in 20 patients with moderate-severe psoriasis, reported good results with mild and easy-to-manage short-term side effects, consistent with those reported in this case. Significant PASI improvement was also shown in the MTX–cyclosporine group compared to the MTX–placebo group. In the study, 14 patients received a short-term combination and 12 of them were successfully treated (2 achieved complete remission). In patients who got a long-term combination, one patient achieved remission, but could not be maintained with monotherapy. Other patients reached PASI 50. This confirms that the MTX–cyclosporine combination is safe and effective for stable plaque psoriasis. No serious irreversible side effects were found (Mohanan et al., 2023).

At the end of the 5-week treatment period using a combination therapy of 7.5 mg MTX tablets per week and cyclosporine tablets 100 mg per day, there was a significant clinical improvement with the disappearance of reddish patches and purulent nodules on the body, as well as the disappearance of pain and hot sensations previously complained by patients. The patient was then given monotherapy in the form of MTX tablets 7.5 mg per week as maintenance therapy to prevent recurrence. Patients admitted high satisfaction with the administration of this combination therapy. Patients experienced mild side effects in the form of nausea and vomiting which could be treated using ranitidine tablets 150 mg per 12 hours and sucralfate syrup 1 tablespoon per 8 hours, so as not to interfere with the sustainability of the main therapy.

CONCLUSION

One case of generalized pustular psoriasis (GPP) was reported in a patient presenting with complaints of purulent lesions distributed throughout the body. The lesions had resolved and frequently recurred for approximately 20 years despite various systemic and topical therapies. Clinical examination revealed generalized erythematous plaques with multiple partially confluent pustules accompanied by scales. Histopathological findings demonstrated neutrophilic collections in the superficial epidermis, focal neutrophilic infiltration, and mild spongiosis, supporting the diagnosis of GPP. The patient was subsequently treated with combination therapy consisting of methotrexate (MTX) 7.5 mg weekly and cyclosporine 100 mg daily, which resulted in significant clinical improvement after five weeks of treatment. The therapy was then continued with MTX 7.5 mg weekly monotherapy as maintenance therapy. During the treatment period, the patient experienced adverse effects of nausea and vomiting, which were managed with supportive therapy consisting of ranitidine 150 mg every 12 hours and sucralfate syrup 1 tablespoon every 8 hours. This case highlights the importance of early diagnosis and appropriate treatment to prevent disease progression, reduce the risk of recurrence, and minimize systemic complications.

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