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Case Report

MULTIPLE TRIGGERING FACTORS OF GENERALIZED PUSTULAR PSORIASIS: A CASE REPORT

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ABSTRACT

Generalized Pustular Psoriasis (GPP) is a rare, severe systemic inflammatory disorder driven by dysregulation of the interleukin-36 (IL-36) pathway. Flares are often precipitated by multiple triggering factors, including infections, medication and underlying comorbidities. A 40-year-old overweight male with a history of pustular psoriasis and poor treatment adherence presented with a severe flare of widespread, painful pustules. The presentation was complicated by consumption of diclofenac and multiple infections, including cellulitis and untreated dental caries, which progressed to septic shock and acute kidney injury (AKI). He was managed with intravenous antibiotics and systemic immunomodulators (cyclosporine, then methotrexate), leading to significant clinical improvement. Host factors like obesity and non-adherence created a pro-inflammatory state, while acute infections and non-steroidal anti-inflammatory drugs (NSAID) acted as potent triggers for IL-36 upregulation, igniting a severe inflammatory cascade. This convergence led to life-threatening systemic complications, underscoring the complexity of the disease. Severe GPP flares are often triggered by a convergence of overweight status, NSAID and acute infections. Effective management requires a holistic, multidisciplinary approach that aggressively identifies and treats all contributing triggers to improve outcomes.

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INTRODUCTION

Generalized Pustular Psoriasis (GPP) represents a rare, severe, and potentially life-threatening systemic inflammatory disorder. It is clinically differentiated from the more prevalent

psoriasis vulgaris, which is characterized by the abrupt and extensive eruption of sterile pustules, comparable in size to pinheads, against a backdrop of painful, inflamed, and erythematous dermis. These pustules frequently merge, resulting in larger purulent accumulations referred to as "lakes of pus," which is a distinctive feature of the disease. These skin manifestations are accompanied by systemic symptoms like high fever and can lead to critical complications, including sepsis and organ failure [1] .

The prevalence of GPP varies globally, with estimates ranging from 1.76 to 124 cases per million people, underscoring its rarity. While it can affect individuals of any age, the typical onset is around 50 years old. The disease's course is often marked by recurrent, unpredictable flares that can be triggered by a variety of factors, including infections, stress, pregnancy, and the withdrawal of systemic corticosteroids[2]. Crucially, the clinical expression, severity, and management of GPP are significantly influenced by multiple factors. Conditions such as metabolic syndrome, cardiovascular disease, and particularly obesity, are increasingly recognized not just as associated conditions but as active contributors to the chronic pro-inflammatory state that primes patients for GPP flares. Obesity, through the secretion of pro-inflammatory adipokines, can directly exacerbate the inflammatory cascades of GPP. Furthermore, acute infections, potent triggers that can provoke severe disease exacerbations by further stimulating cytokine production[3,4].

This case report aims to describe and analyse a severe GPP flare in a 40-year-old overweight male with multiple triggers, including obesity, cellulitis, and untreated dental caries, NSAID trigger, and non-adherence to treatment. This report illustrates the complex, synergistic interplay between these multiple factors and the underlying immunopathology of GPP.

CASE PRESENTATION

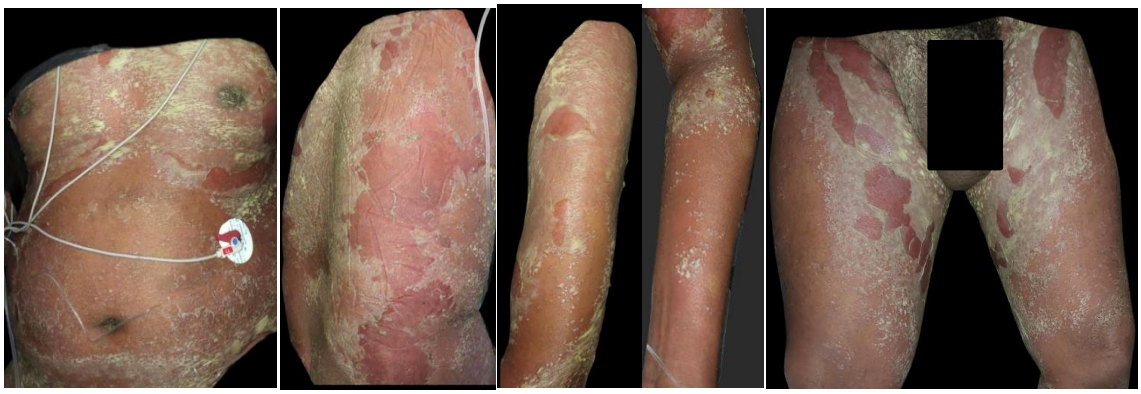
A 40-year-old male went to the emergency department of with an eight-day history of intensely painful, red patches accompanied by the eruption of pus-filled pustules that had spread to nearly his entire body.

The patient had a known history of pustular psoriasis, first diagnosed eight months prior, for which he had been prescribed cyclosporine 150 mg daily. However, he admitted to being non-adherent with his treatment regimen. Seven days before his presentation, he visited a dermatologist private clinic due to swelling and pain in his left leg that had developed after a scratch wound from scratching, and was subsequently diagnosed with cellulitis. He was prescribed a course of diclofenac, clindamycin, and lansoprazole. Just hours after taking the first dose of these medications, he developed erythematous patches that rapidly progressed, with the

emergence of countless pustules over the following two days. This cutaneous eruption was accompanied by systemic symptoms, including high fevers, severe pain in his knees and wrists, nausea, and vomiting. He also noticed uncomfortable, though not painful, white patches on his tongue.

He went to the same private clinic for further treatment and was given systemic steroids and paracetamol. While his fever temporarily improved, the skin lesions worsened, and he developed progressive shortness of breath. One day before admission, the erythema and pustules flared dramatically, spreading across his entire body within hours. His dyspnea became severe, prompting his visit to our emergency department. He denied any use of new herbal remedies or other medications prior to the onset of the cellulitis. A history of untreated dental caries was also noted.

On examination, patient's weight was 92 kg and height 175 cm, corresponding to a BMI of 30 kg/m^2 (overweight). His vital signs were alarming. He had hypotension (99/62 mmHg on norepinephrine 0.2 mcg/kg/min), tachycardia (128 beats/minute), a slight fever of 37.8°C and tachypnea (26 breaths/minute) with high-flow oxygen to keep his oxygen levels at 100%. Dermatological examination revealed multiple sterile pustules situated on well-demarcated, erythematous patches covering the head, neck, trunk, and both upper and lower extremities. In many areas, these pustules had coalesced to form extensive "lakes of pus," with overlying desquamation. The total body surface area (BSA) affected by erythema was estimated at 90%, with a Generalized Pustular Psoriasis Area and Severity Index (GPPASI) score of 48.4 (Severe GPP). Examination of the oral cavity revealed white plaques on the surface of the tongue.



Figures 1. Multiple pustules on erythematous patches, some confluent to form a lake of pus

Laboratory investigations showed significant abnormalities, including marked leukocytosis (24,300/µL) with neutrophilia (77.3%), lymphocytopenia (12.3%), and monocytosis (9.7%). There was evidence of acute kidney injury with azotemia (Urea 51.9 mg/dL; Creatinine 4.64 mg/dL), as well as hyponatremia (132 mmol/L). Inflammatory markers were highly elevated,

including C-reactive protein (23.6 mg/dL) and procalcitonin (>100 ng/mL). A quick Sepsis-related Organ Failure Assessment (qSOFA) score was 2, indicating a high risk for poor outcomes from sepsis. A full SOFA score was subsequently calculated to be 10, correlating with a predicted mortality risk of 10-30%.

Microscopic analysis of the contents of a skin pustule confirmed it was sterile (negative for microorganisms). A microscopic smear from the oral lesions revealed pseudohyphae, confirming a diagnosis of oral candidiasis. A chest X-ray performed during the hospital stay later confirmed the presence of pneumonia, and an abdominal ultrasound revealed cholelithiasis with gallbladder sludge and hepatomegaly. The patient was diagnosed with a severe flare of Generalized Pustular Psoriasis complicated by septic shock, pneumonia, AKI Stage 3, and oral candidiasis.

Initial management consisted of intravenous ampicillin-sulbactam 1.5g twice daily (with the dose adjusted for renal function) to treat the sepsis and suspected bacterial pneumonia, alongside the reinstitution of cyclosporine at a dose of 150 mg daily to control the GPP. Supportive care was provided to manage his hemodynamic instability and respiratory distress.

On the third day of hospitalization, the patient developed persistent nausea and vomiting, which were attributed to cyclosporine. Consequently, cyclosporine was discontinued, and he was started on methotrexate at a low dose of 7.5 mg per week. By this time, his skin had begun to show improvement. After a 10-day course of intensive multidisciplinary treatment, involving dermatologists for the management of pustular psoriasis, internists for systemic support, infection control, hemodynamic stabilization and sepsis care, nephrologists for acute kidney injury management, as well as nutritionists and nursing staff for supportive therapy, the patient's sepsis resolved, his renal function improved, and his skin lesions showed significant resolution. Ultimately, the patient achieved clinical recovery and was discharged in a stable condition on day 10 of hospitalization.

DISCUSSION

GPP is fundamentally a disease of the innate immune system. Unlike psoriasis vulgaris, which is driven by the IL-23/IL-17 T-cell axis, GPP pathogenesis hinges on the dysregulation of the IL-36 cytokine family. IL-36 acts on keratinocytes and immune cells, triggering an intense inflammatory response. In healthy individuals, this pathway is tightly regulated by the IL-36 receptor antagonist (IL-36Ra), a protein encoded by the *IL36RN* gene, which prevents excessive inflammation. In a significant subset of GPP patients, loss-of-function mutations in *IL36RN* lead to a dysfunctional antagonist, resulting in unopposed IL-36 signaling. This unleashes a massive feedback loop of pro-inflammatory cytokine and chemokine production (e.g., CXCL1, CXCL2,

CXCL8), which recruits a vast army of neutrophils into the epidermis. The accumulation of these neutrophils manifests clinically as the sterile pustules that define GPP. Even in patients without a known *IL36RN* mutation, external factors like infections can dramatically upregulate IL-36 expression, leading to a similar pathological cascade[5–7].

The patient's overweight status is a significant contributing factor related to the severity of his disease. Obesity is now understood to be a state of chronic, low-grade systemic inflammation. Adipose tissue is an active endocrine organ that secretes a variety of pro-inflammatory adipokines, including leptin and tumor necrosis factor-alpha (TNF-α). These molecules feed directly into the inflammatory pathways active in psoriasis. Leptin, for example, can exacerbate inflammatory reactions, potentially lowering the threshold for a GPP flare. Therefore, the patient's excess body weight created a baseline pro-inflammatory environment, priming his immune system for the hyper-response that occurred when acute triggers were introduced. This underscores the importance of integrating weight management into the long-term therapeutic strategy for GPP patients with obesity[8].

Infection is one of the most well-documented triggers for GPP flares. Pathogens introduce microbial antigens that activate the immune system, leading to the release of pro-inflammatory cytokines that can tip the delicately balanced immune system into chaos. The cellulitis, likely caused by *Staphylococcus aureus*, was the proximate trigger for this flare. *S. aureus* is known to be a powerful inducer of IL-36 in keratinocytes. IL-36 cytokines are a crucial part of the skin's first-line defense against microbial invaders. In a patient with a pre-existing, dysregulated IL-36 pathway (whether due to genetics or prior disease), exposure to *S. aureus* and its antigens lead to uncontrolled inflammation seen in this case[9].

The patient's history of untreated dental caries represents a crucial triggering factor that should not be overlooked. Dental caries, fundamentally a chronic bacterial infection, acts as a persistent source of inflammation. This aligns with a population-based cohort study in Korea which found a significant association between psoriasis and dental caries, indicating that patients with psoriasis have a higher risk of experiencing dental caries compared to the control group. The study also noted that systemic antipsoriatic treatment might mitigate this risk.[10] **.**

Pneumonia and oral candidiasis secondary infections contributed significantly to the patient's overall systemic inflammatory burden and clinical deterioration into septic shock. Their presence reflects a state of immune exhaustion and dysregulation, where the body, while mounting a hyper-inflammatory response in the skin, is unable to effectively contain infections elsewhere. The systemic inflammation from the pneumonia would further fuel the cytokine storm driving the GPP[11].

While the patient's flare began hours after taking diclofenac (NSAID) and clindamycin, and NSAIDs are reported GPP triggers, it is mechanistically more probable that the severe underlying infection (cellulitis) was the primary driver. The temporal drug association is noteworthy but should be interpreted with caution, as the infection itself is a more potent and direct immunological stimulus[12].

A crucial element in this patient's history is his non-adherence to his maintenance cyclosporine therapy. Poor adherence is strongly associated with more frequent relapses and loss of disease control in patients with GPP. By not taking his immunosuppressive medication regularly, the patient's underlying disease was not adequately controlled, leaving his immune system in a "primed" and hyper-reactive state, making him exquisitely vulnerable to the infectious triggers he encountered[13].

The patient's systemic condition met criteria for sepsis, as evidenced by elevated inflammatory markers and qSOFA/SOFA scores. In this case, AKI were likely multifactorial, with possible contributors including severe systemic inflammation from generalized pustular psoriasis, secondary bacterial infection following cellulitis, as well as hypoperfusion due to septic shock. Septic shock and acute kidney injury further complicated management, necessitating hospitalization and dose adjustments of systemic agents. These factors highlight the importance of a comprehensive approach, prompt recognition and control of infection, careful selection and adjustment of systemic immunosuppressants, hemodynamic stabilization, and renal support are crucial for improving prognosis[14].

The management of severe GPP cannot be focused solely on the skin. It necessitates a comprehensive, rapid, and multidisciplinary approach. The successful outcome for this patient was dependent on the close collaboration between dermatology, intensive care, and likely infectious disease specialists. The patient was considered fit for discharge once sepsis had resolved, with normalization of hemodynamic parameters and no further requirement for vasopressor support. His renal function showed clear improvement, reflected by stabilized levels of urea and creatinine as well as adequate urine output. Dermatologically, there was a marked reduction of pustular and erythematous lesions with GPPASI score 1,5 (mild GPP) and no appearance of new eruptions. In addition, he was able to tolerate oral medications, including methotrexate and other supportive therapies, without significant adverse effects. Finally, the patient was clinically stable, able to maintain adequate oral intake and mobility, and therefore deemed ready to return home. He was discharged safely on the tenth day of hospitalization. The immediate priorities were twofold: stabilizing the patient from septic shock (fluids, oxygen, broad-spectrum antibiotics) and gaining control of the underlying hyperinflammation (with

cyclosporine, then methotrexate). This highlights a key principle: the aggressive treatment of all trigger factors, especially active infections, is as important as the specific GPP therapy itself[15].

CONCLUSION

This case of a 40-year-old overweight male with multiple infections highlights that GPP is a complex systemic disease where outcomes are dictated by far more than just skin pathology. Comorbidities like obesity and non-adherence create a vulnerable, pro-inflammatory state, while acute infections and NSAID act as powerful triggers that can ignite a life-threatening inflammatory cascade. Effective management requires a holistic approach that prioritizes the identification and aggressive treatment of all contributing factors in a collaborative, multidisciplinary setting.

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