


Acute Generalized Exanthematous Pustulosis in a 76-year-Old Man With Neuroendocrine Carcinoma of the Lung, Responsive to Ixekizumab

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Abstract: Acute generalized exanthematous pustulosis (AGEP) is a rare, painful, and pruritic drug-induced rash characterized by sterile pustules on an erythematous base, followed by desquamation. While commonly induced by antibiotics, cases associated with antineoplastic drugs have become more frequent in recent years. Here, we report a 76-year-old Chinese male with lung large-cell neuroendocrine carcinoma who developed erythema and pustules on his left lower leg, which spread to the trunk and limbs after the fourth cycle of immunotherapy and chemotherapy. Despite initial treatments with antihistamines, antibiotics, and systemic glucocorticoids, the patient's condition worsened with the development of extensive pustules and fever. Histopathological and laboratory findings confirmed AGEP, with elevated IL-17 levels. Following the discontinuation of immunotherapy and administration of the anti-IL-17 monoclonal antibody ixekizumab, the patient showed rapid improvement within 5 days, marked by a significant reduction in pustules and normalization of body temperature. This case underscores the role of IL-17 in AGEP's pathogenesis and suggests that IL-17 inhibitors such as ixekizumab may provide an effective treatment option for severe, refractory cases.

Keywords: acute generalized exanthematous pustulosis (AGEP), skin adverse reactions, immunotherapy, ixekizumab

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a painful and pruritic drug-induced skin eruption, characterized by sterile pustules on an erythematous base, followed by desquamation.¹ It is most triggered by antibiotics. Recent reports indicate that immune checkpoint inhibitors (ICIs), such as pembrolizumab and nivolumab, may induce AGEP due to their immunomodulatory effects.² While most cases of AGEP resolve rapidly with systemic corticosteroids, severe or refractory cases may necessitate additional systemic therapies. Drug-induced AGEP is a T-cell-mediated reaction associated with neutrophil activation. Emerging evidence suggests that interleukin-17 (IL-17) plays a key pathogenic role in AGEP and other inflammatory conditions. Elevated IL-17 levels have been detected in some AGEP patients.³ We present a case of AGEP induced by multiple antineoplastic agents, in which clinical symptoms improved rapidly following a single administration of the anti-IL-17 monoclonal antibody ixekizumab.

Case Report

A 76-year-old Chinese man was diagnosed with pulmonary large-cell neuroendocrine carcinoma 7 months prior. For the past 5 months, the patient received monthly immunotherapy and chemotherapy, including pembrolizumab (200 mg), nab-paclitaxel (370 mg on day 1), and cisplatin (35 mg on days 1 to 3). Following the fourth cycle, he developed erythema and pustules on the anterior left leg, accompanied by pruritus and pain, which gradually spread to the trunk and limbs. At another hospital, he was diagnosed with a suspected immune-related cutaneous adverse reaction resembling psoriasis. Treatment with antihistamines, piperacillin-tazobactam, and cefuroxime resulted in partial improvement, permitting continuation of the initial treatment regimen.

Two months earlier, during the seventh cycle of immunotherapy and chemotherapy, the regimen was discontinued due to widespread erythema and pustules. One month earlier, he received bevacizumab (400 mg), etoposide capsules (50 mg twice daily, days 1–10), and radiotherapy for intracranial metastases. Fifteen days later, pustules reappeared on both legs, spread across the body and accompanied by fever (peak temperature 39.2°C). Initial treatment with meropenem (1 g q8h) and moxifloxacin (400 mg daily) for 3 days proved ineffective. The regimen was adjusted to include meropenem (1 g q8h), vancomycin (1 g q12h), intravenous immunoglobulin (IVIG, 0.5 g daily), ganciclovir (0.2 g q12h), and methylprednisolone (40 mg daily). After 3 days, the fever subsided, but the skin lesions showed no significant improvement. Clinical examination revealed pustular eruptions on an erythematous base, distributed across the head, face, neck, axillae, trunk, limbs, and perineum. These pustules had partially coalesced into pus lakes, some of which ruptured, forming extensive bright-red erosive areas with exudation and bleeding. Purpura, ecchymosis, and thick-walled, shriveled blood blisters were observed on the lower limbs, with a negative Nikolsky's sign. Erosion was visible on the mouth and genitals (Figure 1a–f). Laboratory tests revealed elevated white blood cell count ($22.03 \times 10^9/L$, normal range $4.0\text{--}10 \times 10^9/L$), elevated neutrophil count ($18.4 \times 10^{12}/L$, normal range $4.0\text{--}10 \times 10^9/L$), elevated neutrophil percentage of 83.5% (normal range 43–76%), elevated C-reactive protein (98.51 mg/L, normal range 0–5 mg/L), elevated glutamic oxaloacetic transaminase (63.33 U/L, normal range 15–40 U/L), elevated IL-8 (34.83 pg/mL, normal range ≤ 21.4 pg/mL), and elevated IL-17 (24.68 pg/mL, normal range ≤ 20.6 pg/mL). Bacterial examination of the pustules yielded negative results. Histological examination revealed spongiform pustules in the upper layers of the epidermis, with associated hyperplasia of the spinous layer and pestle-like epidermal expansion. Telangiectasia was visible in the superficial and middle dermis, accompanied by perivascular lymphocytic infiltration. The inflammatory infiltrate predominantly consisted of neutrophils, with a small number of eosinophils. Furthermore, fibrin-like deposits were observed in the walls of some local blood vessels (Figure 2a and b). The AGEP European Study Group for Serious Skin Adverse Reactions confirmed a score of 9, supporting the diagnosis of AGEP. Despite the discontinuation of tumor immunotherapy, systemic administration of 40 mg methylprednisolone sodium succinate, and 1 g ertapenem for anti-infective treatment, as well as adjunctive therapies including 1.2 g gamma globulin, topical steroids (fluticasone propionate ointment), antibiotics (fusidic acid cream), ethacridine lactate compresses, and combined helium-neon and neon-helium phototherapy, the rash did not improve, and the levels of inflammatory parameters in the peripheral blood increased (leukocytosis $19.46 \times 10^9/L$, neutrophils $13.92 \times 10^9/L$, C-reactive protein 73 mg/L). As the disease had persisted for 5 weeks, treatment with a single subcutaneous injection of 160 mg ixekizumab was initiated. Within 5 days, although the inflammatory parameters remained elevated (leukocytes $16.88 \times 10^9/L$, neutrophils $11.44 \times 10^9/L$, C-reactive protein 56 mg/L), the patient's skin improved significantly, and the pustules had largely disappeared. After 13 days, only slight redness was visible (Figure 3a–c). At the follow-up visit, 2 months after discharge, no new flare-ups were observed.

Discussion

AGEP is a rare but potentially life-threatening cutaneous reaction primarily caused by drugs.¹ Drugs commonly associated with AGEP include aminopenicillins, quinolones, macrolides, sulfonamides, terbinafine, and diltiazem.⁴ With the increasing use of tumor immunotherapy, reports of immunotherapy-related drug dermatitis have gradually risen. Matsubara et al⁵ reported that pembrolizumab in combination with chemotherapy for squamous cell carcinoma caused AGEP in patients. Although pembrolizumab is not typically associated with AGEP, its mechanism as a PD-1 inhibitor enhances T-cell activity, which could theoretically promote the development of AGEP. However, a clear causal relationship remains unclear. Drug-induced dermatitis caused by bevacizumab has also been reported.^{6–8} AGEP symptoms typically resolve within 15 days after discontinuation of the causative drug. Even after the drug is stopped, the immune response it induces can keep the immune system activated. T-cells and other immune cells may continue to release inflammatory mediators, perpetuating the inflammatory response and delaying lesion resolution. In this case, the patient developed erythema and pustules with pruritus and pain on the anterior surface of the left lower leg after the fourth round of immunotherapy and chemotherapy for pulmonary large cell neuroendocrine carcinoma. The symptoms of the skin lesions gradually spread to the trunk and limbs, improving after treatment with antihistamines and antibiotics. Two months later, during the seventh round of immunotherapy and chemotherapy, the patient's rash worsened, with widespread erythema and several pinhead-sized pustules visible on the erythematous base, accompanied by itching, multiple oral ulcers, and fever. The patient had a high AGEP score, no personal or family history of psoriasis or psoriatic arthritis, and no recurrence of pustular lesions during follow-up. Combined with the medication history and histological findings of spongiform pustules and eosinophils, the diagnosis of AGEP is likely.⁹ However, due to the complex medication history, it is challenging to



Figure 1 (a-f) Patient condition at the time of admission. The patient presents with pustular eruptions on the head, face, neck, bilateral axillae, trunk, limbs, and perineum. Some pustules coalesced into larger pustular lakes and collapsed, forming extensive bright red erosive surfaces with exudate and blood. Blood blisters on the lower limbs were atrophic with thick walls. Purpura was also observed on the legs, and Nikolsky's sign was negative. Erosive lesions were present in the oral and genital regions.

pinpoint the exact cause of AGEF, as it could have resulted from immunotherapy, chemotherapy, or antibiotics. Distinguishing AGEF from generalized pustular psoriasis (GPP) can be particularly challenging, as both conditions exhibit nearly identical clinical features, such as widespread pustules and erythema. The pathogenesis of AGEF remains unclear, but it is believed that drug- or infection-induced activation of T-cells plays a crucial role. Studies indicate that keratinocytes and drug-specific CD4+ T lymphocytes in AGEF secrete cytokines such as interleukin-8 (IL-8), IL-17, IL-36, tumor necrosis factor-alpha (TNF- α), and granulocyte-macrophage colony-stimulating factor (GM-CSF), which induce neutrophil aggregation in the epidermis, leading to the onset of the disease.^{10,11} Kabashima et al¹² found that peripheral blood Th17 cells and the cytokine IL-22 are elevated in AGEF patients, and that IL-17 and IL-22 synergistically stimulate keratinocytes to produce IL-8. IL-8 may contribute to epidermal damage by causing neutrophil accumulation. Navarini et al¹³ suggested that mutations in the IL-36RN gene could be implicated in

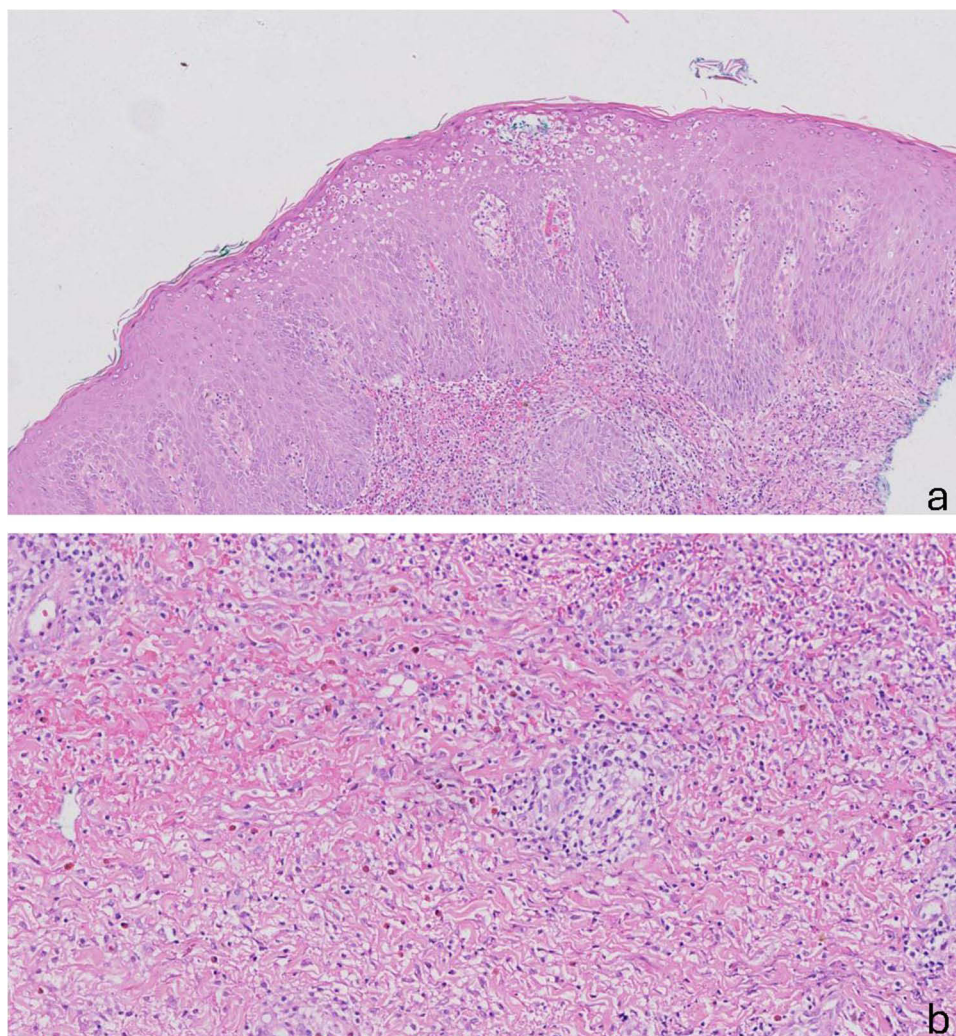


Figure 2 Histological examination. Spongiform pustule formation was observed in the epidermis, with diffuse infiltration of neutrophils and scattered eosinophils in the superficial dermis using Hematoxylin-Eosin stain (a, $\times 100$; b, $\times 200$).

the pathogenesis of AGEp. Additionally, Nakai et al¹⁴ showed that Th17 cell activation leads to increased IL-36 levels, and due to IL-36RN mutations, IL-36 signaling becomes uncontrolled, potentially leading to AGEp. Several case reports and small clinical studies have shown the efficacy of spesolimab, an anti-IL-36 receptor monoclonal antibody, in treating AGEp, particularly in patients who do not respond to conventional therapies such as corticosteroids and immunosuppressive agents.^{15,16} Ixekizumab, a high-affinity monoclonal antibody targeting IL-17A, has also been reported to be effective in treating hydroxychloroquine-induced AGEp.¹⁷ Our patient had severe and prolonged disease with elevated inflammatory markers such as white blood cells, neutrophils, C-reactive protein, IL-8, and IL-17. Pathological examination revealed sub-corneal pustules and neutrophil infiltration, suggesting that ixekizumab may be an appropriate therapeutic option, given its positive effects in inflammatory skin diseases with neutrophil infiltration, such as pyoderma gangrenosum and Netherton's syndrome.^{18,19} While spesolimab offers promising treatment for severe AGEp, its high cost limits its widespread use, making ixekizumab a more accessible and cost-effective alternative. IVIg is another effective non-pharmacological option with a favorable safety profile, particularly in the setting of active infection or malignancy. However, due to the cost of repeated infusions, IVIg is typically used early and followed by another treatment.¹⁹

It is important to note that this patient developed AGEp following the administration of multiple antineoplastic agents, making it challenging to identify immunotherapy as the sole causative agent. Drug-induced AGEp is often complex, involving multiple medications with varying immunomodulatory effects. While ICIs have increasingly been associated with AGEp due to their immune activation, chemotherapy agents and other concomitant medications cannot



Figure 3 (a-c) Patient's condition after treatment. Large areas of erythema were observed on the head, face, neck, both axillas, trunk, both upper limbs, and perineum. The pustules on the entire body were essentially dried up, with significant desquamation.

be entirely excluded as contributing factors. The recurrence or exacerbation of symptoms after antibiotic administration suggests that antibiotics may have played a role in either triggering or exacerbating the reaction, aligning with previous reports of antibiotic-induced AGEP. Given these uncertainties, clinicians should promptly discontinue any suspected offending drugs and initiate timely symptomatic treatment, such as systemic corticosteroids and supportive care, to manage severe cutaneous reactions and prevent complications. A multidisciplinary approach, involving dermatologists, oncologists, and immunologists, is essential for optimizing management strategies and ensuring patient safety, particularly in cases of severe or refractory AGEP.

In conclusion this case highlights the potential role of ixekizumab in the treatment of severe AGEP in the setting of cancer treatment.

Data Sharing Statement

All data used in this work are publicly available.

Ethical Approval

The ethical committee of the hospital gave the agreement to report this case.

Consent Statement

The reporting of this study conforms to the CARE guidelines. Ethical review and approval was not required to publish the case details in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient for publication of this case report and any accompanying images as per our standard institutional rules.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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