

The Confusion between Pustular Psoriasis and Acute Generalized Exanthematous Pustulosis as a Cause of Exfoliative Dermatitis: A Case Report

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ABSTRACT

Background: Pustular psoriasis and Acute Generalized Exanthematous Pustulosis (AGEP) are grouped under pustular diseases, in which their clinical manifestations are similar. Those diseases can lead to exfoliative dermatitis. **Purpose:** To evaluate a specific histopathological examination in differentiating Pustular Psoriasis and AGEP. **Case:** A 55-year-old woman presented with sudden redness and diffused scaly skin with multiple pustules and also fever. She had taken Cefadroxil 2 days before the scales and pustules appeared. Leukocytosis and histopathological examination results from biopsy supported the diagnosis of AGEP. The patient was then hospitalized and received steroid therapy. Within the first week of tapering off, the scales disappeared but the pustules increased. After such clinical findings, the histopathological examination results were revisited and reassessed. Thus, we considered changing the diagnosis to Pustular Psoriasis, and the therapy was switched to Methotrexate. The patient had a better outcome, and the pustules slowly disappeared entirely. **Discussion:** It is often difficult to differentiate between the pustules in pustular psoriasis and AGEP unless by thorough history-taking and physical examinations. AGEP is characterized by a widespread of pustules with an acute febrile onset; while pustular psoriasis is an acute variant of psoriasis where pustules are spread over erythematous skin and accompanied by high fever and leukocytosis. **Conclusion:** Histopathological examination is the gold standard for the establishment of pustular psoriasis diagnosis. The histopathological characteristics of pustular psoriasis and AGEP are difficult to differentiate. Therefore, we need detailed history-taking and physical examination to establish the diagnosis.

Keywords: *Psoriasis pustulosa, AGEP, histopathological examination, human and disease.*

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BACKGROUND

Psoriasis is a chronic inflammatory skin disease, with a strong genetic basis, characterized by complex alterations in epidermal growth and differentiation and multiple biochemical, immunologic, and vascular abnormalities, and a poorly understood relationship to nervous system function. Psoriasis is divided into three categories in accordance with different clinical presentations: erythrodermic/pustular psoriasis, guttate psoriasis, and chronic plaque psoriasis.¹ The etiology of psoriasis remains unclear, although there is evidence for genetic predisposition. The role of the immune system in psoriasis causation is also a major topic of research. A research article reported a role of autoantigen in psoriasis, such as LL37 SBG Tcell autoantigen, ADAMTSL5 (a melanocytic protein), and Keratin17.² Psoriasis can also be provoked by external and internal triggers, including mild trauma, sunburn, infections, systemic drugs, and stress.³

There are several clinical subtypes of psoriasis including the uncommon pustular variants, which are subdivided into generalized and localized forms. These subtypes vary in their presentations, but all have similar histopathologic characteristics.⁴ Pustular psoriasis is slower in onset, its pustules occurring on top of an erythematous base. Often, the pustules coalesce into large, purulent collections. Generalized pustular psoriasis has been associated with pregnancy, drugs, and infection. In addition, there is often a personal or family history of psoriasis.⁵

One of the pustular psoriasis differential diagnoses is drug eruption, particularly cutaneous drug eruption. Severe cutaneous drug reactions include a wide spectrum of clinical manifestations ranging from a mild morbilliform cutaneous rash to severe forms of hypersensitivity.⁶ Special attention was given in this report to the acute generalized exanthematous pustulosis (AGEP) which is a severe

cutaneous adverse reaction characterized by the rapid development of non-follicular, sterile pustules on an erythematous base induced in 90% of cases by the use of systemic drugs.^{5,6} Histologic features of AGEP are characterized by intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema containing neutrophilic and eosinophilic infiltrates. The majority of intraepidermal pustules are located in the upper epidermis, often contiguous with the subcorneal pustules. The pustules tend to be large and contain eosinophils.⁵

AGEP can be difficult to differentiate from generalized pustular psoriasis (GPP) both clinically and histopathologically. Clinically, signs of AGEP include abrupt onset, short duration, polymorphous lesions, association with recently consumed drugs and spontaneous healing after their elimination, non-recurrence, and absence of arthritis or a personal or family history of psoriasis. Histopathological differentiation of AGEP from GPP has not been well documented and some even consider a distinction based strictly on dermatopathology to be impossible.⁷

Both pustular psoriasis and AGEP can lead to a condition called exfoliative dermatitis. It is defined as diffuse erythema and scaling of the skin involving more than 90% of the total body skin surface area. Prognosis is variable, and it depends primarily on the underlying etiology. Drug-induced exfoliative dermatitis (ED) has the best prognosis while malignancy-associated ED has the highest mortality.⁸ For some of human diseases, establishing the diagnosis is not always simple. We reported a challenging case in addressing the diagnosis between pustular psoriasis and AGEP in a patient presented with exfoliative dermatitis. This case reveals a specific histopathological examination in differentiating pustular psoriasis and AGEP. This report discusses the clinical presentation and diagnosis, emphasizing histopathological examination and treatment.

CASE REPORT

A 55-year-old female was referred to the Emergency Department of dr. Soetomo General Academic Hospital on March 2018, with red scaly patches on almost all over the body that lasted for a week. Pustules were present over patches on the left leg and stomach. The lesion suddenly appeared after consuming Cefadroxil that was prescribed for sore throat medication. The lesion firstly appeared on her arm and then spread all over her body. The rash was pruritic, slightly painful and accompanied by fever. At the initial days of onset, she did not immediately visit a physician for treatment but only consumed coconut

water. One week later, she went to another hospital. Furthermore, she also complained about the scale on her scalp that often appeared.

Five months before she was hospitalized, she suffered from an itchy sensation in her lower legs, then it became red skin with blisters filled with pus, which was similar to the presented pustules on the inferior extremities. Past medical history included diabetes mellitus type 2 and with Glibenclamide as the longstanding treatment. The use of irritant soap, joint pain, recurrence, or food and drug allergy were absent. During the admission, the patient looked unwell. The physical examination of general state showed a blood pressure of 110/80 mmHg, pulse rate of 98 times per minute, respiratory rate of 21 times per minute, and body temperature of 37.9°C. From the head and neck, there was no sign of anemia, cyanosis, icterus, or dyspnea. The thorax examination results showed that the heart and lungs were normal. From abdomen, liver and spleen were not palpable. From her upper and lower extremities, edema, subungual hyperkeratosis, and pitting nail were absent but there were warm on palpation. There was no enlargement of the cervical, axillar, inguinal, and genital lymph nodes.

Dermatological examination on the chest, back, abdomen, upper and lower extremities showed erythematous macules with indistinct margins covered with thin scale. There were pustules over the erythematous macule on the left leg and the stomach. No geographic tongue was noted. Nikolsky's sign was negative, and the mucous membranes were unaffected.

The laboratory examination on March, 2018 revealed that the hemoglobin level was 12 g/dL, with leukocytosis $13.490 \times 10^9/L$ (normal range $4.0-11.0 \times 10^9/L$), and neutrophilia $11.4 \times 10^9/L$ (normal range $1.70-7.50 \times 10^9/L$), renal and liver function were normal, fasting blood glucose 282 mg/dL, HbA1C 9.4%. The urinalysis results revealed showed brown color with protein +1, glucose +1, ketone +2, bilirubin +1, erythrocytes 10-15/high power field (hpf), urobilinogen +1, leucocyte 5-50/hpf. The pustules were sterile from microorganisms.

A 5-mm punch biopsy was taken from the patient's left leg, and such size of biopsy was chosen to achieve a representative sample. Histopathological examination shows a prominent, relatively large, subcorneal pustules were observed, which were filled with neutrophils. The neutrophils extended into the underlying epidermis, which shows a sign of spongiosis, parakeratosis, and elongation of rete ridges. The papillary dermis was slightly edematous, and there was a moderately dense perivascular

inflammatory infiltrate consisting of lymphocytes, histiocytes, and a predominance of neutrophils. There was an associated extravasation of red blood cells.



Figure 1. A-E. The dermatology state before treatment showed diffuse erythema patches covered with scales on facial region, thoracalis and abdomen region, thoracalis posterior region. F-G. There were no pitting nails.

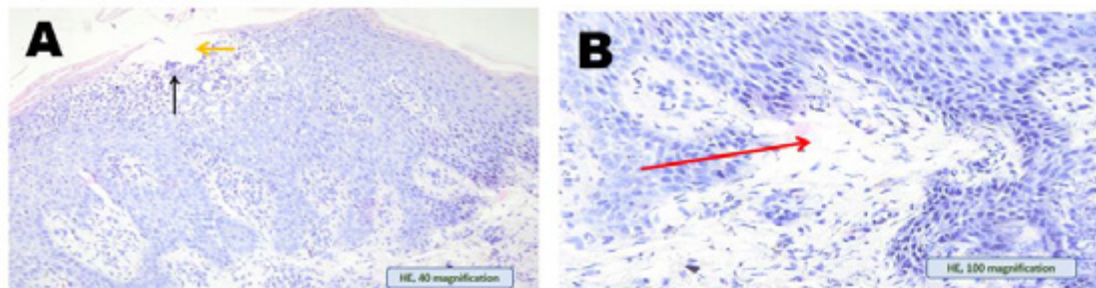


Figure 2. Histopathology examination of the skin lesion taken from the left leg. Demonstrates: A. A relatively large prominent subcorneal pustules (yellow arrow) filled with a dense exudate of acute inflammatory cells along with a few acantholytic cells (black arrow) (Original magnification 40x). B. Blood vessel dilations (red arrow) surrounded by lymphocytic infiltration. Staining was applied with hematoxylin and eosin (Original magnification 100x).

The differential diagnosis included AGEP, and subcorneal pustular dermatosis (Sneddon-Wilkinson disease). Hence, the patient was treated for AGEP with emollients and oral steroids. There was an improvement after 3 days, with further improvement over the following days, the sheets of pustules sequentially disappeared from her lower leg and stomach. However, 1 week after tapering off, her skin condition worsen. There had been no new drug

administration in this period. Pinhead pustules developed on the scaly erythematous patches over the patient's trunk and limbs. A new biopsy was not taken at this point, as the morphology was identical to that of the previous eruption, but we reviewed the previous histopathologic examination results. Finally, it lead to a possible diagnosis of pustular psoriasis as a clinical diagnosis and methotrexate 15mg (5 mg every 12 hours) a week orally was started, and within 2 weeks

the scales and pustules had disappeared, leaving post-inflammatory hyperpigmentation. The dose of methotrexate was decreased to 12.5 mg followed by a

further decrement of 2.5mg every week as the patient's skin had cleared gradually. The patient was discharged and followed-up in the outpatient clinic.

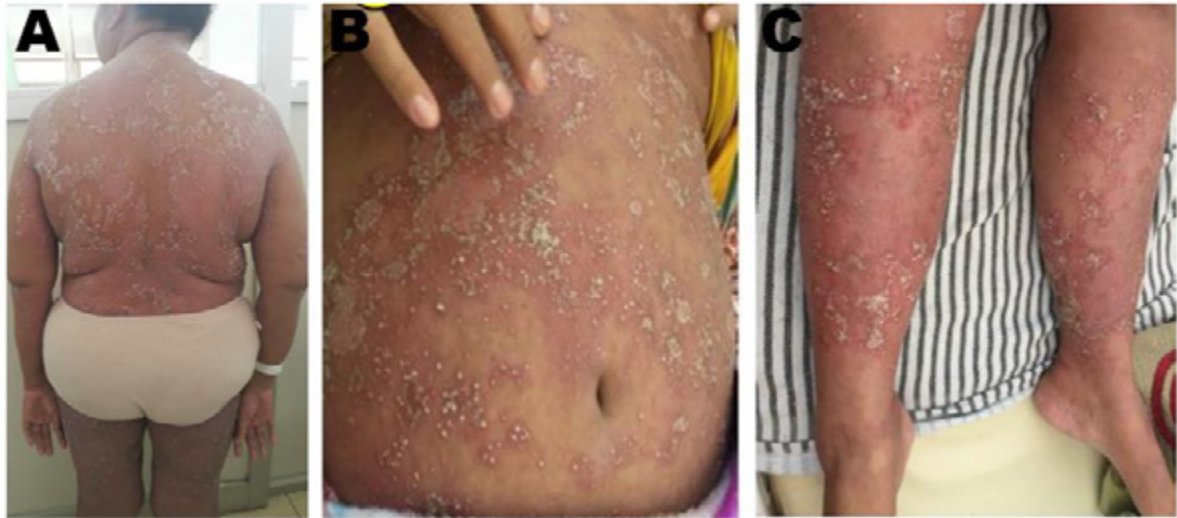


Figure 3. A-C. After tapering the steroid off, there were multiple pustules on erythematous patches flared up and spread to another part of the body.



Figure 4. A-H. The dermatology state after 4 weeks of treatment, no more pustules and scales were found, but the erythema still present.

DISCUSSION

AGEP is an acute febrile eruption that is often associated with leukocytosis and can be present as an adverse drug reaction commonly associated with aminopenicillins, followed by quinolones, hydroxychloroquine, sulfonamides, terbinafine, diltiazem, ketoconazole, and fluconazole. The lesions often start on the face or major skin creases. Generalized desquamation occurs approximately 2 weeks later. The estimated incidence of AGEP is approximately 1–5 cases per million per year. The period from drug exposure to reaction onset is typically within 48 hours, with antibiotics having a median of 24 hours. Infectious agents such as parvovirus B19, *Chlamydia pneumoniae*, and cytomegalovirus are infrequently related etiologically. Additional causes of AGEP, such as contact with mercury and spider bites have been described.^{5,9}

There seems to be a correlation between the mutations in the *IL-36RN* gene, encoding the interleukine-36 receptor antagonist (IL-36Ra), and the development of generalized pustular eruptions after drug intake. IL-36Ra has an anti-inflammatory function, and it blocks the proinflammatory cytokines IL-36 α , IL-36 β , and IL-36 γ . Mutations in the *IL-36RN* gene can result in uncontrolled IL-36 signaling and increase the downstream production of further proinflammatory cytokines and chemokines.¹⁰ However, it is still unclear if mutations in *IL-36RN* lead to AGEP or, rather, to a drug-induced generalized pustular psoriasis (GPP), as it is described in some cases.¹¹

AGEP has been classified as a T cell-related sterile neutrophilic inflammatory response (type IVd reaction). The activation, proliferation, and migration of drug-specific cluster of differentiation (CD) 4 and CD8 T cells play an important role in the development of AGEP. It is supposed that drug-specific cytotoxic T cells and cytotoxic proteins such as granzyme B and perforin induce the apoptosis of keratinocytes, leading to subcorneal vesicles. Recently, it has also been shown that granulysin is also expressed by CD4 and CD8 T cells and natural killer (NK) cells in different drug reactions including AGEP, suggesting that granulysin may also play a role in the pathogenesis of AGEP. Furthermore, in-vitro tests have shown that drug-specific T cells in AGEP patients produced significantly more chemokine (C-X-C motif) ligand 8 (CXCL8)/IL-8, a potent neutrophil chemotactic chemokine. CXCL8/IL-8 is thought to play a central role in the formation of pustules by the recruitment of neutrophils. The increased levels of IL-17 and IL-22, as well as granulocyte-macrophage colony-stimulating factor (GM-CSF) in AGEP patients, may

also participate in the strong neutrophilic activity by the synergistic effect on the production of CXCL8/IL-8 and the prevention of apoptosis of the neutrophils. Recent studies also described a higher level of IL-17 expression by neutrophils, mast cells (MC), and macrophages, and a lower level by T cells, in AGEP patients.¹²

Differential diagnosis of AGEP includes pustular psoriasis, hypersensitivity reaction with pustulation, subcorneal pustular dermatosis (Sneddon–Wilkinson disease), pustular vasculitis, or in severe cases of AGEP, toxic epidermal necrolysis.⁵

Histologic features of AGEP are characterized by intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema containing neutrophilic and eosinophilic infiltrates. The majority of intraepidermal pustules are located in the upper epidermis, often contiguous with the subcorneal pustules. The pustules tend to be large and contain eosinophils. Spongiform changes occur in both the intracorneal and subcorneal pustules. Epidermal changes also include spongiosis with exocytosis of neutrophils and necrotic keratinocytes.⁵

The main management of AGEP is the discontinuation of the causative agent. Considering that it is mostly benign and self-limiting, a supportive treatment based on topical steroids and disinfectant solutions for the pustules and rehydrating lotions during the desquamative phase is usually sufficient.⁵

Psoriasis is a common disease, occurring more frequently with advancing age, and estimates of the prevalence of psoriasis in adults ranged from 0.51% to 11.43%.¹³ Common triggers were systemic steroids, pregnancy, and upper respiratory tract infections. A positive family history of psoriasis and GPP was sometimes present. Comorbidities included obesity, hypertension, hyperlipidemia, and diabetes mellitus.¹⁴ Pustular psoriasis is classified into GPP and localized pustular psoriasis. GPP includes acute GPP, pustular psoriasis of pregnancy, and infantile/juvenile pustular psoriasis. Localized pustular psoriasis includes palmoplantar psoriasis and acrodermatitis continua of Hallopeau (ACH).⁴ General pustular psoriasis is a distinctive acute variant of psoriasis. It is usually preceded by other forms of the disease. Attacks are characterized by a fever that lasts several days and a sudden generalized eruption of sterile pustules 2–3 mm in diameter. The pustules are disseminated over the trunk and extremities, including the nail beds, palms, and soles. The pustules usually arise on highly erythematous skin, first as patches and then becoming confluent as the disease becomes more severe. With prolonged disease, the fingertips may become atrophic. The erythema that surrounds the

pustules often spreads and becomes confluent, leading to exfoliative dermatitis. Acute GPP is often associated with systemic symptoms such as fever, chills, malaise, anorexia, nausea, and severe pain.

Other physical findings may be present with acute GPP, such as subungual pustules and geographic tongue.^{1,15}

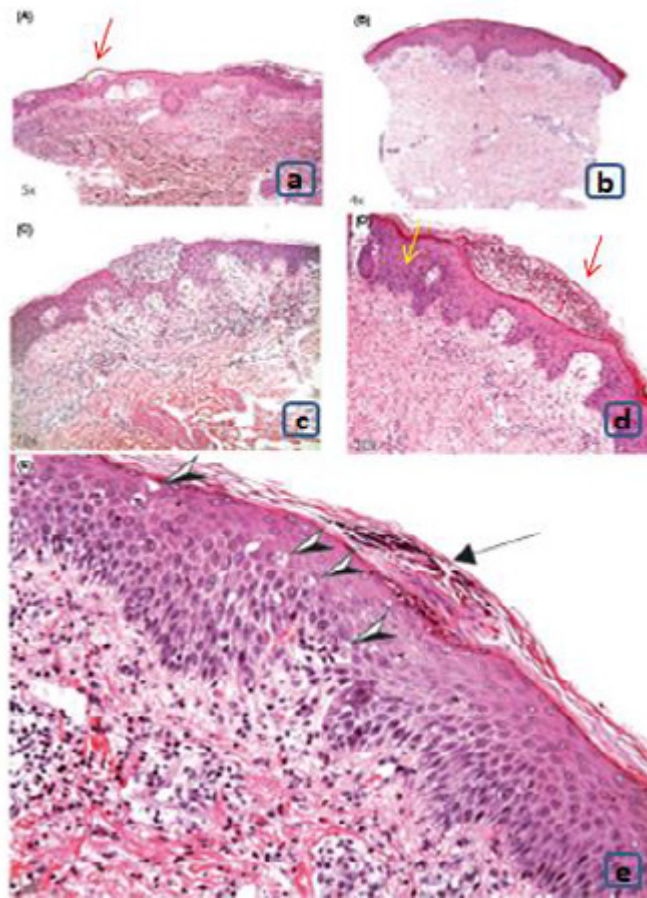


Figure 5. Histopathology of acute generalized exanthematous pustulosis. A. Spongiform pustules (red arrow) at various epidermal levels (Hematoxylin and eosin, original magnification: 50x). B. Slightly spongiform subcorneal macro-pustule with a superficial and (lower) mid-dermal, perivascular and interstitial dermal infiltrate (Hematoxylin and eosin, original magnification: 40x). C. Slightly spongiform subcorneal-intraepidermal pustule, minor acanthotic rete ridge changes, spongiosis, neutrophilic exocytosis, papillary edema, and a mixed perivascular and interstitial infiltrate (Hematoxylin and eosin, original magnification: 100x). D. Subcorneal macro-pustule (red arrow), slightly acanthotic rete ridge changes (yellow arrow), papillary edema, dilated papillary vessels, mixed perivascular and interstitial infiltrates (Hematoxylin and eosin, original magnification: 200x). E. Small sub-/intraepidermal pustule contiguous with a Munro-like abscess (black arrow), spongiosis, few epidermal necrotic keratinocytes (arrowheads), erythrocyte extravasation, discrete leukocytoclasia, and mixed perivascular and interstitial infiltrate including eosinophils. Hematoxylin and eosin, original magnification: 200x).⁷

Pustular psoriasis is characterized by the increased expression of IL-1 β , IL-36 α , and IL-36 γ transcripts. Nevertheless, IL-17 signaling is also involved in pustular psoriasis and patients with generalized pustular psoriasis without IL-36R mutations responded to anti-IL-17 treatments.^{12,16} Activation of neutrophils is a basic observation in GPP. However, in GPP the primary

abnormality seems to reside in keratinocytes/T lymphocytes rather than in the neutrophils.⁷

The recommended first-line therapy for GPP in adults is acitretin, cyclosporine, or methotrexate. Acitretin is preferred as the first-line agent with a recommended dose of 0.75 to 1 mg/kg/d. Patients typically respond within 7 to 10 days of oral retinoid therapy. A maintenance dose of 0.125 to 0.25 mg/kg/d should be continued for several months to prevent a

recurrence. However, methotrexate and cyclosporine are recommended as good alternatives. Methotrexate can be started with a test dose of 2.5 mg and then gradually increase the dose until a therapeutic level is achieved (average range, 10–15 mg weekly; maximum, 25–30 mg weekly). Cyclosporin has shown efficacy in patients with GPP at doses of 2.5 to 5 mg/kg/d. There is some evidence to indicate that methotrexate is slightly more effective than cyclosporine. Although the data are based on small

case reports and series, infliximab is considered by many experts to be first-line therapy especially in patients with extensive disease.^{17,18}

Differentiating AGEPP from GPP, especially acute GPP, presents a clinical and histopathological challenge. Whereas no single histopathological feature is decisive on its own, the combination of features and their grade of severity can substantially contribute to negotiating this differential diagnosis successfully.

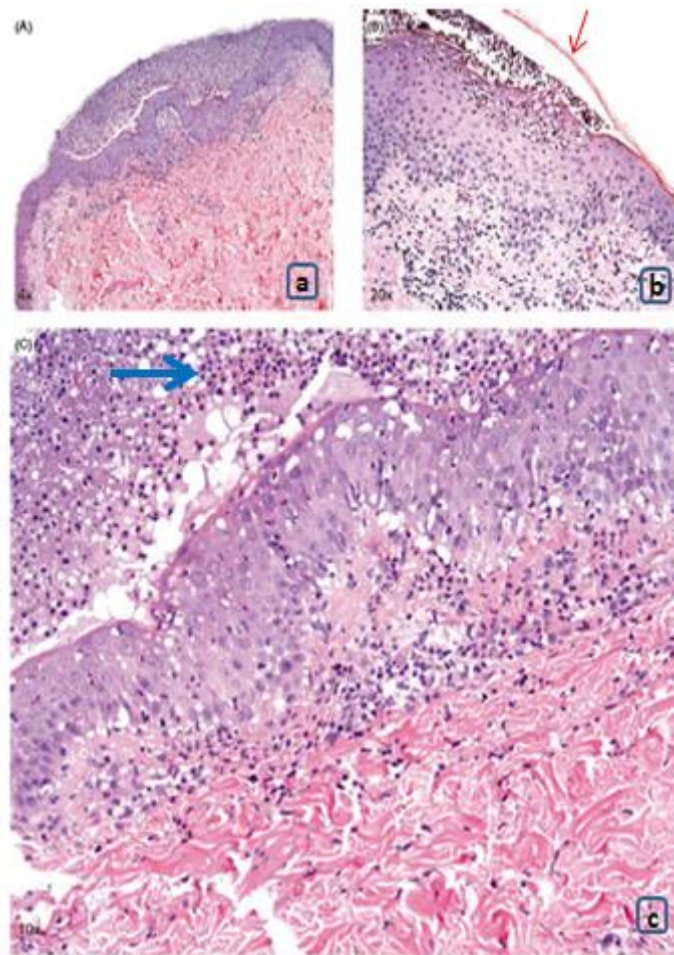


Figure 6. Histopathology of acute generalized pustular psoriasis A. Subcorneal macro-pustule, neutrophilic exocytosis, superficial perivascular, mainly mononuclear, infiltrates with papillary neutrophils (Hematoxylin and eosin, original magnification: 40x). B. Subcorneal/intraepidermal spongiform macro-pustule of Kogoj (red arrow), neutrophilic exocytosis, slightly psoriasiform rete ridge changes, and dilated papillary vessels (Hematoxylin and eosin, original magnification: 100x). C. Detail macro-pustule: neutrophilic exocytosis, papillary neutrophils, and superficial perivascular, mainly mononuclear infiltrate (blue arrow) (Hematoxylin and eosin, original magnification: 200x).⁷

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