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Case Report

Acute generalised exanthematous pustulosis, an atypical presentation of severe leptospirosis

急性泛發性發疹性膿皰病，一宗嚴重鉤端螺旋體病的非典型表現

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Background: Acute generalised exanthematous pustulosis (AGEP) is a condition associated with acute onset of fever with numerous non-follicular pin head sterile pustules on an erythematous background, commonly precipitated by drugs. Infections have been occasionally associated with AGEP. Leptospirosis is a zoonotic infection due to *Leptospira spp*. We are reporting as far as we are aware, the first case of leptospirosis-induced AGEP. A 33-year-old Malay woman presented with acute febrile, generalised pin-point pustular skin eruptions on an oedematous erythematous background, multi-organ dysfunction and haemodynamic instability. She recovered well with penicillin-group of antibiotics, skin care and supportive management. Leptospira DNA RT-PCR test was positive.

急性泛發性發疹性膿皰病是一種伴隨急性發熱的皮疹，在紅斑上有著許多針頭大小非濾泡的無菌膿皰，多數是由藥物引起，偶爾可以是感染相關的。鉤端螺旋體病是由鉤端螺旋體屬引起的人畜共通傳染病。現報告我們所知的第一例鉤端螺旋體病引起的急性泛發性發疹性膿皰病。一名33歲的馬來女性患有急性發熱，並全身發出伴有水腫和紅斑背景的針頭大小膿皰性皮疹，另有多重器官衰竭和血行動力循環不足。她的病情在獲處方青黴素類抗生素，皮膚護理和支持性治療後恢復良好。鉤端螺旋體的脫氧核醣核酸轉錄聚合酶連鎖反應測試呈陽性。

Keywords: Acute generalised exanthematous pustulosis, Febrile rash, Infection, Leptospirosis, Severe cutaneous adverse drug reaction

關鍵詞：急性泛發性發疹性膿皰病、發熱性皮疹、感染、鉤端螺旋體病、嚴重皮膚藥物不良反應

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Introduction

Acute generalised exanthematous pustulosis (AGEP) is a rare adverse cutaneous adverse reaction characterised by an acute onset of numerous non-follicular sterile pustules on a diffuse erythematous background, mostly precipitated by drugs. Infections, spider bites and mercury exposure have been at rare instances reported as the cause of AGEP.[1] Leptospirosis is a zoonotic infection due to *Leptospira spp*, which is

underreported in many countries due to a lack of clinical awareness and early diagnostic facilities.[2] It may present with variable and non-specific clinical manifestations mimicking other febrile illnesses, including fever, headache, myalgia, conjunctival suffusion, rash (i.e. maculopapular or petechiae), jaundice or other organ involvement. Most of the cases of leptospirosis are mild and self-limiting, while some are severe and potentially fatal. Herein, we report the first occurrence of AGEP triggered by leptospirosis presenting with septic shock and multi-organ dysfunction.

Case presentation

A 33-year-old Malay woman, with no past significant medical history, presented with fever for three days associated with generalised cutaneous erythema and pruritus for two days. She denied any recent new drug intake before onset of the rash. She had no history of psoriasis or other skin diseases and also had no known drug allergy history. She denied recent travelling and there was no family history of cutaneous disease.

On examination, she was jaundiced, severely dehydrated and lethargic, febrile with a temperature of 40°C, tachycardic (130 beats/min) and hypotensive (77/50 mmHg). She had bilateral conjunctivitis and generalised non-follicular distributed pustules on a background of oedematous erythema, mainly over the intertriginous areas (Figures 1 and 2). Oral and genitalia mucosa, scalp and nail examination was unremarkable. Systemic examination was normal. Laboratory studies showed marked leucocytosis 29.9 (4.0-11.0x10^9/L) with neutrophilic predominance 28.97 (2.0-7.5x10^9/L). She suffered from acute kidney injury [Urea: 16.8 (2.5-7.2 mmol/L), creatinine 256 (53-97 μmol/L)], acute liver injury [total bilirubin 99.7 (3.4-20 μmol/L), aspartate transaminase 68 (5-34 U/L)] and coagulopathy [INR: 1.48 (<1.0)]. Platelet count was 186 (150-400x10^9/L).

Blood, urine and tissue cultures were negative. *Mycoplasma pneumoniae* serology and *Legionella pneumophila* urine serology were negative.

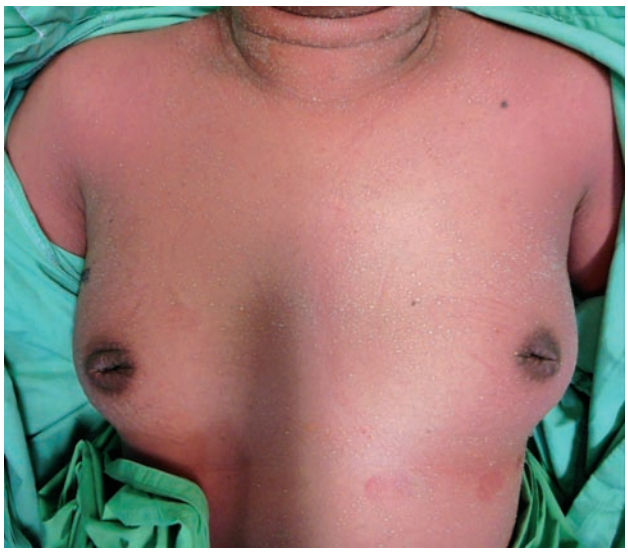

Figure 1. Generalised non-follicular distributed pustules on a background of oedematous erythema, mainly over the major intertriginous area (neck and axilla).

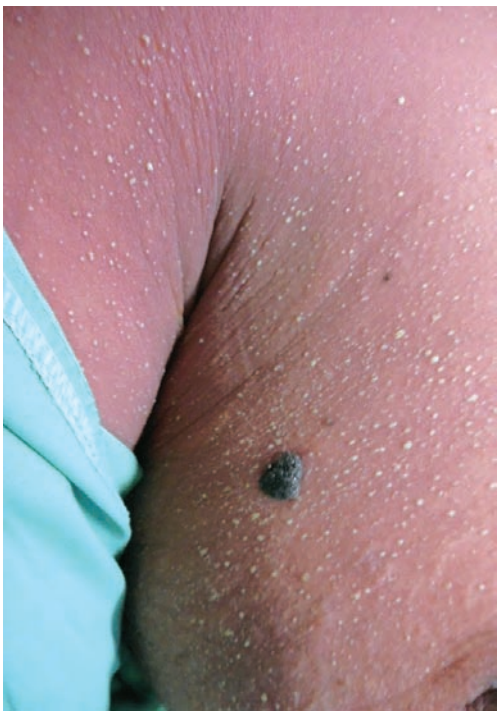

Figure 2. Closer view over the right axilla, showing crops of pinpoint pustules on a background of oedematous erythema.

Leptospira DNA RT-PCR was positive, consistent with the diagnosis of leptospirosis.

A skin biopsy was performed in view of clinical differential diagnosis of AGEP, pustular psoriasis, subcorneal pustular dermatosis, extensive cutaneous candidiasis and meningococcemia was suspected. Histopathology found spongiform subcorneal pustule with papillary oedema (Figure 3).

Intensive management as per sepsis-6 guideline and a broad spectrum antibiotic, piperacillin-tazobactam was commenced. For skin care, potassium permanganate was prescribed as an astringent followed by intensive emollients during the desquamation stage. She responded well to the treatment given and became haemodynamically stable after receiving the first dose of intravenous antibiotic. The cutaneous lesions resolved within a few days, followed by widespread desquamation. The antibiotic was changed to amoxicillin-clavulanic acid on day 5, after reviewing her blood culture. She was discharged well after completion of seven days of antibiotic with no sequelae.

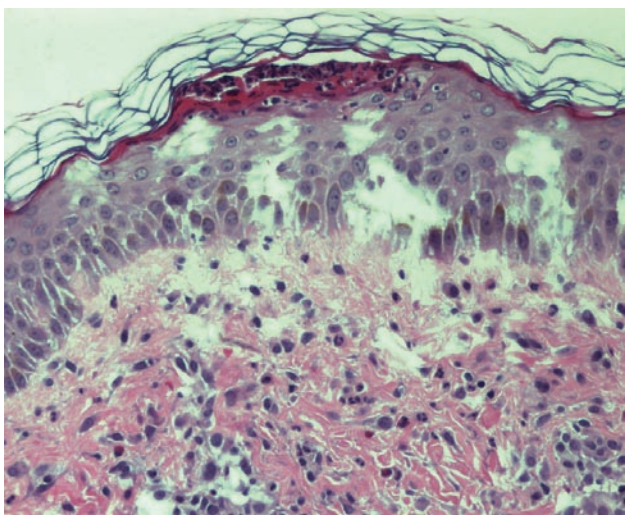

Figure 3. Epidermis showing spongiosis with neutrophilic pustules within the subcorneal layer. The papillary dermis shows mild neutrophilic and lymphoplasmacytic cell infiltrate with occasional eosinophils (Haematoxylin and eosin stain, original magnification x 200).

Discussion

AGEP is frequently known as a severe cutaneous adverse drug reaction (SCAR). It is characterised by numerous tiny pustules on a background of erythematous skin. The commonest drugs leading to AGEP are antibiotics (i.e. pristinamycin, aminopenicillins, quinolones, sulphonamides and macrolides) and antiepileptic medications (e.g. carbamazepine, phenobarbital, phenytoin and lamotrigine).[3] Other drugs that are reported included allopurinol, terbinafine, hydroxychloroquine, and diltiazem.[3] Viruses (i.e. *Human parvovirus B19, Cytomegalovirus, Epstein-Barr Virus, Coxsackie and Mumps*), and bacteria (i.e. *Mycoplasma pneumoniae, Chlamydia pneumoniae, Escherichia coli*), have been reported as rare causes of AGEP. As far as we could identify, there are less than 20 case reports.[4-8]

The onset of skin eruption usually develops within hours or up to two days after exposure to the causative agent. It typically starts over the major intertriginous zones, trunk and upper extremities. Nikolsky's sign may be positive during the early stage, when the pustules coalesce, whereas only post-pustular desquamation is observed in the late stage. This condition is often self-limiting and usually resolves spontaneously within two weeks after the causative agents have been removed.

EuroSCAR retrospective AGEP-scoring is a validated, scoring system for the diagnosis of AGEP (Table 1).[9] Summing up the score makes a maximum score of 12 and a minimum of 0. The higher the score, the more likely it is AGEP. Our patient fulfilled all the criteria, scoring a 12, which confirmed the diagnosis of AGEP.

The main differential diagnoses in our case are generalised pustular psoriasis (GPP), subcorneal pustular dermatoses (SPD), extensive cutaneous

Table 1. EuroSCAR retrospective AGEP scoring-system[11]

Morphology	POINTS
Pustules	
Typical	2
Compatible	1
Insufficient	0
Erythema	
Typical	2
Compatible	1
Insufficient	10
Distribution/Pattern	
Typical	2
Compatible	1
Insufficient	0
Post-pustular desquamation	
Yes	1
No/Insufficient	0
Evolution	
Mucosal involvement	
Yes	-2
No	0
Acute onset (<10 days)	
Yes	0
No	-2
Resolution (<15 days)	
Yes	0
No	-4
Fever ≥38°C	
Yes	1
No	0
Neutrophils ≥7000/mm^3	
Yes	1
No	0
Histology	
Other disease	-10
No representative/no histology	0
Exocytosis of neutrophils	1
Subcorneal and/or intraepithelial spongiform or not pustule(s) with or without papillary oedema	2
Spongiform subcorneal and/or intraepithelial pustules with papillary oedema	3

Total score ranges from: 0=no AGEP; 1-4=possible; 5-7=probable; 8-12=definite

candidiasis. Cases of GPP usually have a chronic course and histologically, there is acanthosis and papillomatosis. Subcorneal pustular dermatoses is a rare, chronic, relapsing pustular eruption involving the trunk and the intertriginous area. The epidermal and papillary spongiosis in this patient makes the diagnosis of SPD unlikely. Cutaneous candidiasis typically affects immunocompromised patients and fungal bodies should be seen over the subcorneal area histologically. In our case, there was absence of the satellite pustules or maceration on the skin.

The immune-pathogenesis of leptospirosis is the subject of ongoing research. Our body's innate immune system consists of immune cells resident to the local tissue including T cells, dendritic cells, PMNs, mast cells, NK cells and their cytokines. It is postulated that after the *Leptospira spp.* breaches the dermal layer of host system, these cells recognise the *Leptospira* specific receptors to trigger an immune response and phagocytosis.[10] In our case, leptospirosis may have triggered the innate immune system which then activated the cytotoxic T cells resulting the immunological cascade contributing to AGEP.

Leptospirosis is a zoonosis caused by pathogenic spirochaetes of the genus *Leptospira spp.* with feral and domestic animals being the reservoir. Humans are infected through contact of mucous membrane or skin with water, soil or vegetation infected by urine of infected animals. Jaundice, purpuric rashes, cutaneous haemorrhagic rash, continual desquamation and intense pruritus are the common skin manifestations reported. Other than pruritus, our patient presented with AGEP which is an atypical cutaneous manifestation of leptospirosis.

AGEP typically manifests with only fever and neutrophilia. Nevertheless, there have been few reported cases of drug-induced severe AGEP mimicking septic shock.[11,12] The severity of leptospirosis depends on the *Leptospira* strain or serovar involved, inoculum size for the strains;

age, health and immune status of the infected individual. Our patient presented with atypical AGEP with severe systemic involvement resulting in haemodynamic instability and multi-organ impairment. The combined effect of leptospirosis infection and AGEP which have disrupted the innate and adaptive immunity might have contributed to such a severe systemic manifestation. Further research is warranted to determine the contributing factors to the severity of AGEP and its relationship with leptospirosis. However, given the rapid clinical response to antibiotic treatment, we may postulate that leptospirosis infection may play a more important role than AGEP in contributing to our patient's disease severity.

With prompt discontinuation of offending agents, supportive care and topical skin nursing care, prognosis for patients with AGEP is excellent. Systemic corticosteroids have been reported to provide immediate haemodynamic stability and clinical improvement in a few cases of resistant severe AGEP not responding to supportive management. However, our patient improved dramatically with appropriate antibiotic treatment and hence systemic corticosteroids were not initiated.

In conclusion, severe leptospirosis should be considered as one of the triggering factors of AGEP, particularly in endemic tropical countries.

Declaration

Competing interest: The authors declare that they have no competing interests
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