False Alarm: Cutaneous Anthrax Suspicion in a Case of Bullous Erysipelas - The Clinicopathological Consideration

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Abstract: Erysipelas is acute superficial infection involving the epidermal and dermal layers, which may feature bullous formation. Bullous erysipelas lesion can mimic Sweet's syndrome, pyoderma gangrenosum and other skin and soft tissue infections (SSTIs). A 42-year-old male presenting with multiple erythematous and edematous plaques with a large bulla on his left lower leg was first diagnosed clinically with Sweet's syndrome or pyoderma gangrenosum. Routine histopathology showed partial epidermal necrosis and massive dermal edema with neutrophils, lymphocytes and nuclear dust, which might be consistent with the aforementioned diagnoses. However, taking into account the clinical presentation, the possibility of cutaneous Anthrax was also raised, especially when the patient was later found to work in areas where domesticated animals roamed. Further investigation with Gram staining did not demonstrate Gram-positive bacilli, negating the suspicion. Cefadroxil as prophylaxis which later continued with clindamycin gave marked improvement. Clinical and histological findings, and response to antibiotics favored bullous erysipelas as the final diagnosis.

1 INTRODUCTION

Erysipelas is an acute superficial infection and inflammation of the skin, that features a painful, warm, erythematous swollen lesion, with sharply demarcated border. Systemic signs and symptoms include fever, nausea, vomiting, general weakness, muscle pain, and lymphedema. (FY Chong et al., 2008). Usually involving epidermal and dermal layers, 5% of erysipelas can be complicated by bulla formation which represents deep seated process, such as in bullous erysipelas.(S Vichitra et al 2016)
Bullous erysipelas lesions were characterized by erythematous macules and patches with flaccid epidermal sterile blister. (S Vichitra et al 2016). Usually appears on facial areas and legs, they can be accompanied with necrosis and purpuric hemorrhage which take longer period of tissue repair.

Not only difficult to treat and related to more complications, bullous erysipelas with atypical presentation can mimic other disease, such as Sweet's syndrome, pyoderma gangrenosum, and other skin and soft tissue infections (SSTIs) that are diagnostically challenging. Histopathology examination shares many similar features among erysipelas and those diseases, including cutaneous anthrax. Therefore, clinical recognition coupled with knowledge of pathology of diseases contribute greatly to making sound diagnosis. We present a case of challenging diagnostic approach in a case of bullous erysipelas that was nearly mistaken for cutaneous anthrax.

2 CASE

A 42-year-old male came to our department's outpatient clinic presenting with several painful erythematous lesions on the rightlower leg on March 2017.They had appeared since approximately 10 days before. A blister had appeared some days after and a tentative aspiration was performed at another hospital. However, the lesion became ulcerated.The patient was feverish and his lower leg was swollen. Previous treatment comprised of amoxycillin-clavulanic acid and non steroidal anti-inflammatory drug. History of trauma, skin lesion, or application

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of substances was denied, as was history of diabetes mellitus, hypertension, malignancy, alcohol and smoking. The patient worked in the municipal sanitary and environmental department, mostly behind the desk but regularly supervised workers in the region.

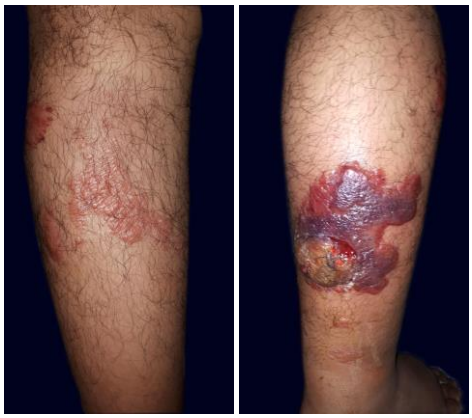

Figure 1.Purpuricand erythematous plaques with a large hemorrhagic blister on the right lower leg. Swelling was noted.

There were purpuric and erythematous plaques on the right lower leg, with extensive edema. A large hemorrhagic blister was present in the area where a puncture was previously done. Vital signs and general physical examination were normal, except for BMI of 32.92 kg/m^2. Laboratory result were also in normal ranges, except increase in erythrocyte sedimentation rate/ESR (74 mm/hour) and low eosinophil count (0,9%).Swab from the hemorrhagic base of the blister showed few Gram-positive cocci and leukocytes. Aworking diagnosis of Sweet's syndrome with differential diagnosis of pyoderma gangrenosum was made.

Biopsy was performed on two sites, the erythematous plaque on the anterolateral leg and the blister margin. Patient received cefadroxil 500 mg twice a day for a week after biopsy and continued with clindamycin 300 mg for possible infection. Hematoxylin and eosin staining from both sites demonstrated severe upper dermal edema leading to blister formation, perivascular lymphocytes and neutrophils, and erythrocyte extravasation. Necrosis of epidermis and adipocytes in some parts was noted. These histopathology findings alerted us of the likelihood of cutaneous anthrax. Patient were reexamined for possible infection of anthrax. Patient acknowledged there were many domestic animals (i.e. goat) where he worked, but no history of direct contact previously before the lesion appeared. There was no report of similar casein the environment where he worked.

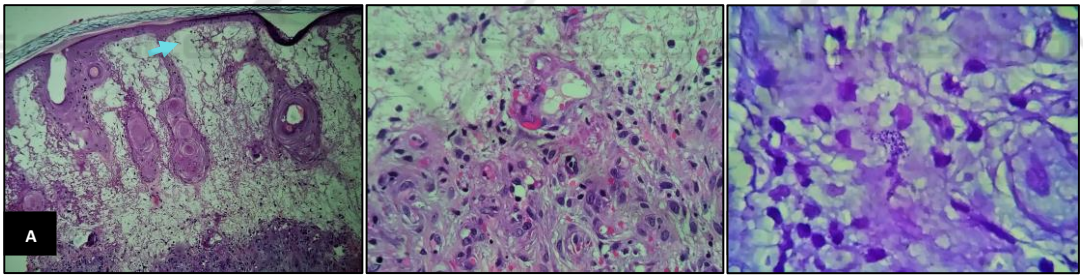

Figure 2. A. Marked edema on the upper dermis (blue arrow) and destruction of hair follicles (H&E,100x). B. Infiltrate of inflammatory cells in dermal layer consisted of neutrophils, lymphocytes, nuclear dusts, and few eosinophils with endothelial impairment and erythrocytes extravasation (pink arrow) (H&E, 1000x).C. No bacilli were found in Gram stain. Structures resembled Gram-positive coccus (yellow arrow) sparsely distributed in dermal layer (Gram, 1000x).

Special staining did not reveal Gram-positive bacilli which did not support diagnosis of cutaneous anthrax and showed what looked like Gram-positive cocci, suggesting the more likely cause of infection for bullous erysipelas.

Ultrasonography by vascular surgeon concluded lymphedema, although d-dimer and fibrinogen test result were in normal limits, which did not support deep vein thrombosis. Patient was suggested to wear compression stocking. The condition gradually improved with systemic antibiotics, and additional treatment with normal saline wet dressing and sodium fusidic ointment. Clindamycin already given as prophylaxis and was continued for another two weeks after biopsy until all lesions resolved and leaving residual hyperpigmentation. The patient was finally diagnosed with bullous erysipelas.

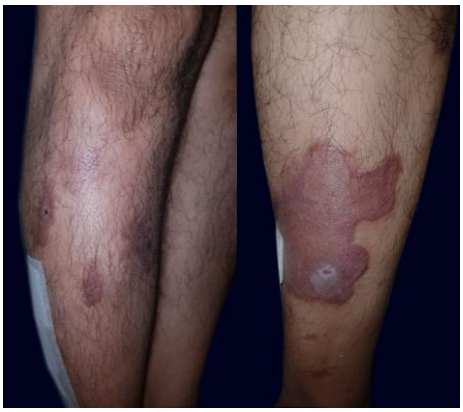

Figure 3. Evaluation after biopsy and receiving antibiotics revealed marked improvement. Erythema and edema subsided.

3 DISCUSSION

There was slight difficulty in assessing the condition that we believe was due to non-classical clinical presentation that might be interpreted as non-infectious in origin, such as Sweet's syndrome and pyoderma gangrenosum. Sweet's syndrome (SS) lesion is characterized by tender, glistening erythematous plaque that gives the impression of vesiculation, while pyoderma gangrenosum (PG) may have several variances, including ulceration with violaceous border. (Cohen PR et al., 2016; Cowell FC et al., 2008).However, disease history and clinical data did not support the two entities.

Initially, infection was not considered because there was no known trauma preceding the lesion. The lesions appeared abruptly and accompanied by fever and pain which was first thought to be clinical manifestation of Sweet's syndrome. There was history of blister aspiration which later exacerbated lesion. Moreover, there was no history of malignancy, systemic infection, medication, or inflammatory bowel disease which were usually found in SS.(Cohen PR et al., 2016). Pyodermagangrenosum usually occurred in older people, with various underlying morbidity, that was still doubtful in our case. Nevertheless, it was diagnosis of exclusion that required ruling out other diseases.(Cowell FC et al., 2008).

Regional lymph node enlargement and edema, however, might suggest underlying infection. Laboratory result did not support leukopenia and neutropenia, although there was higher result of erythrocyte sedimentation rate.(Cohen PR et al., 2016). Our case showed low neutrophil count which was not consistent with infection and SS.

Bullous formation, along with abscess, hemorrhagic purpura and necrotic lesion are major local complications usually found in erysipelas. Local complication occurred around 31-52% patients with erysipelas. It is associated with several risk factors, including age ≤ 50 years, female gender, obesity, smoking, history of diabetes mellitus, hypertension, heart disease, and prior treatment with non-steroidal anti-inflammatory drug. (Krasagais KI et al., 2006). A comparison study in 2015 between erysipelas patients with localized complication and without showed history of antibiotic before admission (OR = 5.15) and accelerated erythrocyte sedimentation rate (OR = 5) as independent risk factors. (Montravers P et al., 2016). Our case was obese and had history of short-course amoxicillin-clavulanic acid and anti-inflammatorymedication.Possible sources of infection in erysipelas including leg ulcer, excoriating skin disease, and ascending infection from distal limb inoculation, which usually follow toe-web fungal infection. (Jendoubi F et al., 2019). Since we did not find any signs mentioned above in our case, we assumed the more likelihood of microtrauma as the source of inoculation. As we could not ascertained the origin of infection in our case, the diagnosis of Sweet's syndrome was considered. The ulceration had confused the diagnosis of erysipelas with pyodermagangrenosum.

Histopathological evaluation unfortunately did not give conclusive result. The main findings, heavy neutrophilic infiltrates corresponding with epidermal necrosis and stark dermal edema, suggestive of infection, but might also support the provisional diagnoses.(Johnston RB et al., 2012). Striking edema and epidermal necrosis combined with description of blister formation and subsequent ulceration also alerted us of cutaneous anthrax possibility. .(Johnston RB et al., 2012). Gram-positive bacilli, however, was not found.

Blood cultures in bullous erysipelas usually produce negative result. Culture can be performed by bacterial swab from the blister or ulcer, even though there are still more possibilities of negative finding. (Krasagais KI et al., 2006). performed culture of bullous erysipelas and find 4 out of 7 patients were sterile. We did not perform it since he initially was diagnosed as SS and PG.

Reexamination of the patient did not confirm history of direct contacts with domesticated animals (i.e. goats) or their products, even though he acknowledged some of those animals wandered

around the neighborhood where he sometimes came to inspect. To his knowledge, there was no similar ailment reported from the area or by his co-workers. Moreover, cutaneous anthrax lesion usually starts with papule and vesicles distributed on the face or upper extremities that rapidly breaks down to necrotic painless ulcer with brawny edges, unlike in our case. Antigen detection by tissue polymerase chain reaction (PCR) is highly recommended to perform if cutaneous anthrax is still suspected.(Titou H et al., 2012) Suspicion of cutaneous anthrax can also be excluded by immunohistochemistry, although it was not available.

Finally, a favorable response toward antibacterial monotherapy and leg compression as adjuvant without the need to add systemic corticosteroid has greatly supported diagnosis of bullous erysipelas. Erysipelas in general has rapid and favorable response to antibacterial treatment. Although many guidelines has been established, treatment of SSTIs including erysipelas with local complication is still challenging because there were many variants, degree and different etiologic agents which associated with various pathomechanisms of infections and clinical manifestation.(E Silvano et al., 2016) Because SSTIs in general usually due to Gram-positive microorganism, first line recommended treatment are usually broad spectrum antibiotics with more susceptibility towards Gram-positive bacteria, such as β-lactams, cephalosporin and clindamycin.(Edwards J et al., 2006). However, many guidelines available do not consider target population and its geographical differences, which is related to epidemiology of various bacterial strains and susceptibility toward certain antibiotics.[7] Clindamycin was chosen to treat this patient due to its broad-spectrum activity since the infection covered deeper structures of the skin and its underlying structures. Clindamycin and several antibiotics have its antitoxin property that is beneficial to reduce early release of exotoxins from Gram-positive microorganism, since toxin production is associated with streptococcal and staphylococcal infections. (Montravers P et al., 2016).Guideline for SSTIs management from Infectious Diseases Society of America (IDSA) recommends the use of clindamycin for mild to moderate erysipelas and other non-purulent SSTIs.(Stevens DL et al., 2014). Dosage option and adjustment should be considered based on specific clinical condition such as renal insufficiency.

4 CONCLUSION

Bullous erysipelas is a skin and soft tissue infection characterized by blistering and is not an uncommon entity. However, it may still be unrecognizable if the source and mode of infection cannot be identified. Its clinical presentation could mimic other entities, such as Sweet's syndrome, pyoderma gangrenosum, and cutaneous anthrax, each with its own characteristics (e.g. pseudo vesiculation, brawny edges) and underlying condition that should not be overlooked. Histopathology may at times show findings that are indistinguishable so that correlation with clinical information should always be sought.

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