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Case Report

Orthopaedics Section

Necrotising Cutaneous Lesions in Anti Neutrophil Cytoplasmic Antibodies- Associated Vasculitis Mimicking Necrotising Fasciitis

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ABSTRACT

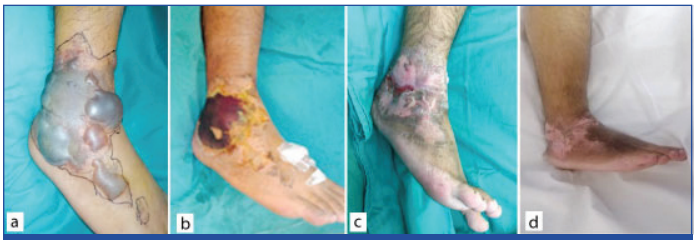
Necrotising vasculitis is a very rare occurrence and commonly caused by an underlying autoimmune pathology. Anti Neutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis is an established cause for cutaneous manifestations of necrotising vasculitis, and is associated with multisystemic involvement, in which presentations of one system may feature predominantly and lead to misdiagnosis. A 33-year-old male presented with acute history of shortness of breath and necrotising blisters over both his ankles and arms. He was initially provisionally diagnosed with necrotising fasciitis, which was eventually ruled out as the serological biomarkers (including low level of C3 and presence of cytoplasmic type of ANCA on indirect immunofluorescence) drew suspicion of an autoimmune pathology. A multidisciplinary approach led to the commencement of steroid, which improved the patient's condition rapidly. The histological examination of sample from the skin biopsy later confirmed the diagnosis of ANCA-Associated Vasculitis (AAV). The patient eventually recovered with excellent outcomes. Despite its rarity, any abnormal skin lesion may be a subtle presentation of necrotising cutaneous vasculitis. A high index of suspicion through a multidisciplinary approach, coupled with meticulous investigative process including serological biomarkers and skin biopsy, helps to avoid misdiagnosis which may be detrimental to the patient.

Keywords: Blisters, Skin biopsy, Steroid

CASE REPORT

A 33-year-old male presented to the Casualty Department with an acute episode of dyspnoea, accompanied by a one day history of sudden swelling with skin lesions over his both ankles and both arms. The skin lesions were rapidly progressing in size and extension along the limbs. He was a recent consumer of an unknown traditional medication meant to improve his working stamina and recently ventured into tropical rainforest as part of his job as a forest ranger. There was no history of trauma nor penetrating wound injury to the limbs.

Physical examination revealed an afebrile, tachypnoeic patient. Local examination found multiple erythematous blisters over anterolateral aspect of both ankles, and over lateral aspect of both arms [Table/Fig-1,2]. The right ankle and arm appeared to be worse than the contralateral side. The underlying compartments of the limbs were soft and the surrounding subcutaneous tissue was oedematous but not tense. There was no purpuric or nodular lesion accompanying the blisters, nor there was any crepitus on palpation. The neurovascular status was intact for all limbs, with distal pulses recorded at normal volume.



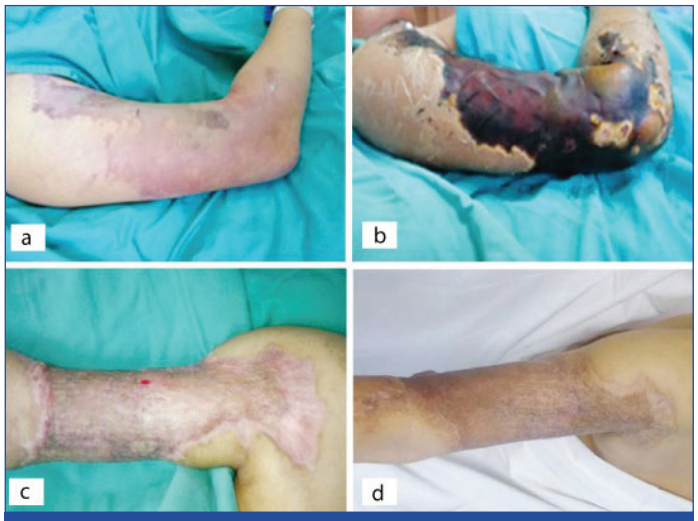
[Table/Fig-1a-d]: The clinical images of the right ankle showing gradual progression from the admission (a) until at one year after the presentation (d). (a) Necrotising blisters which are localised at the anterolateral aspect of right ankle and foot; (b) After commencement of the steroid and without any surgical debridement, the skin lesion became superficial dry necrotic patch; (c) After removal of the necrotic patch, dressing was done and granulation tissue gradually healed; (d) The skin over the anterolateral aspect of the ankle completely healed without any residual wound.

Initial laboratory investigations then showed elevated total white cell count (20.3×10^9/L) with thrombocytopenia (95×10^9/L); deranged renal (urea 21.8 mmol/L, creatinine 432 µmol/L, sodium 127 mmol/L and potassium 5.7 mmol/L) and liver functions (total bilirubin 19 µmol/L, alkaline phosphatase 324 IU/L, alanine aminotransferase 102 IU/L, aspartate aminotransferase 39 IU/L and albumin 16 g/L); and severe metabolic acidosis on arterial blood gas sample (pH 7.337 and serum bicarbonate 12.9 mEq/L). Erythrocyte Sedimentation Rate (ESR) was 112 mm/hr and C-Reactive Protein (CRP) reading was 18 mg/L. Urgent ultrasonogram of the right arm and ankle was done and found only subcutaneous oedema with no focal collection, debris or presence of abscess.

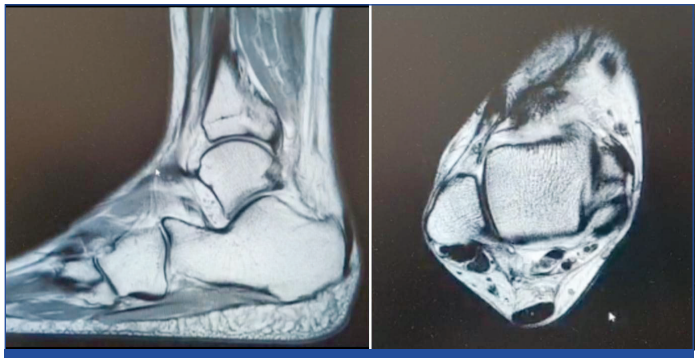
The patient's condition rapidly deteriorated within a few hours as the metabolic acidosis worsened (arterial blood glass pH 7.229 and serum bicarbonate 9.8 mEq/L), and he was intubated for ventilatory support. He became haemodynamically unstable and developed shock, requiring commencement of an inotrope. He also developed jaundice (total bilirubin 28 µmol/L), and due to the worsening urea (25.5 mmol/L) and creatinine (522 µmol/L) level, the intensive care team commenced continuous venovenous haemodialysis to improve the renal function. The blisters worsened rapidly in thickness and colour, and the surrounding skin became indurated. However, the lesions were still localised at the original sites and did not extended to adjacent skin. An initial diagnosis of sepsis with necrotising fasciitis was made by the attending internal medicine team, and vancomycin (300 mg every 8-hourly) was started as an empirical antibiotic. The patient was then referred to the orthopaedic team.

The rapid progression and systemic manifestation rendered a suspicion of a more aggressive underlying systemic autoimmune disorder. A thorough assessment using Magnetic Resonance Imaging (MRI) of the right arm and ankle was done [Table/Fig-3] which only confirmed the earlier findings of subcutaneous oedema on ultrasonogram. A bedside probe test was thereafter done, with a small incision of around 1.5 cm long was made at the overlying skin

on the right ankle and arm. The underlying fascia was found to be healthy, and this negative probe test dispelled the initial diagnosis of necrotising fasciitis. Tissue culture sent from this bedside test also grew no organism.



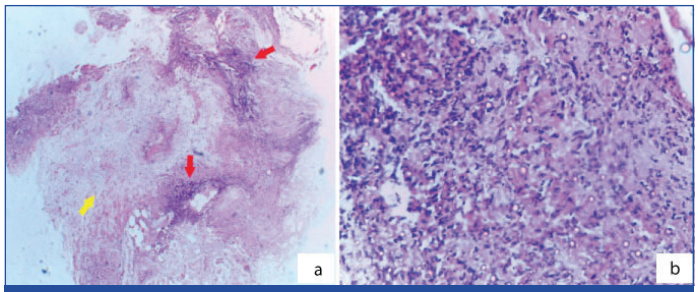
[Table/Fig-2a-d]: The clinical images of the right arm showing gradual progression from the admission (a) until at one year after the presentation (d).
(a) Erythematous, raised skin lesion which rapidly developed into necrotising blisters over the anterolateral aspect of the right arm; (b) Similar like the right ankle, the extensive skin lesion did not progress further at adjacent regions, and eventually became necrotic patch without any surgical debridement; (c) Due to its large size, after removal of the necrotic patch, split skin grafting (SSG) was done for soft tissue coverage; (d) The skin completely healed without any residual wound over the anterolateral aspect of right arm.



[Table/Fig-3]: The sagittal (left) and coronal (right) view of the Magnetic Resonance Imaging (MRI) of the right ankle showed only presence of subcutaneous oedema of around the ankle. The muscular striation appeared normal and there was no breach of the fascia, hence suggesting the lesions did not extend beyond the fascia and confined to the skin and subcutaneous tissue.

Further work ups to investigate the possibility of autoimmune disorder revealed positive cytoplasmic type (c-ANCA) and low serum level of Complement-3 (C3). The serum level of Complement-4 (C4) was however within the normal range. A diagnosis of AAV with systemic involvement of cutaneous, renal, pulmonary and hepatic systems was preliminarily made. A skin biopsy was then done. A multidisciplinary discussion was held between the internal medicine, orthopaedic and intensive care teams, which were at the crossroad in deciding to prescribe glucocorticoid for the treatment of AAV, as steroid may further suppress the immune system and may aggravate the patient condition since infection was also suspected. A decision for trial to start low dose of intravenous hydrocortisone (15 mg every 12-hourly or 0.5 mg/kg/day), combined with the earlier commencement of vancomycin, was made. As there was improvement on patient's general condition especially his renal (urea 19.7 mmol/L and creatinine 398 µmol/L) and pulmonary (arterial blood glass pH 7.340 and serum bicarbonate 16.2 mEq/L) functions, the appropriate-for-weight dosage of hydrocortisone (30mg every 12-hourly) was given 24 hours after the initial dose. This precaution was proven to be diligent as the blood culture later yielded growth of streptococcus pyogenes.

The patient's condition rapidly improved and he was extubated after three days of commencement of the steroid, with his pulmonary (arterial blood glass pH 7.395 and serum bicarbonate 19.8 mEq/L) and liver (total bilirubin 17 µmol/L, alkaline phosphatase 124 IU/L, alanine aminotransferase 72 IU/L and aspartate aminotransferase 26 IU/L) functions markedly improved. Although his renal function improved and stabilised, the patient still required haemodialysis throughout the admission. The diagnosis of AAV was confirmed and supported by the result of the skin biopsy- histologically, it was reported to demonstrate features of necrotising vasculitis including granulomatous inflammation surrounding the vessels, with neutrophilic infiltration showing leukocytoclastic activity and fibrinoid necrosis [Table/Fig-4]. The vancomycin was stopped after seven days, with repeated blood culture yielded no growth. The hydrocortisone was continued for 10 days, and then changed to low dose oral prednisolone (10 mg per day for the first 2 weeks, and subsequently tapered down to 5 mg daily).



[Table/Fig-4]: The histopathology image using low magnification (H&E 10x); (a) Showing heavy presence of neutrophilic infiltration (red arrows) surrounded by fibrinoid necrosis (yellow arrow). The high magnification (H&E 40x) image; (b) confirms vascular infiltration by the leukocytoclastic activity.

Without surgical debridement, the skin lesions gradually resolved. The ruptured blisters however left superficial dry necrotic patches [Table/Fig-1b,2b], which was then removed at three weeks after admission. Split Skin Grafting (SSG) was done over the right arm and ankle to facilitate early healing [Table/Fig-1c,2c]. The patient subsequently recovered with normal pulmonary and liver functions. The regular haemodialysis of three sessions per week eventually improved his renal function, although some irreversible damage rendered his creatinine level to remain between the range of 150 to 200 µmol/L. Two months after he was discharged from the hospital, he did not required haemodialysis anymore as instructed by the nephrologist. He completed the low dose oral prednisolone for three months. Currently one year after the admission, he has recovered with no limitation of activities, including those involving the usage of his limbs [Table/Fig-1d,2d].

DISCUSSION

Necrotising vasculitis is a very rare occurrence and characterised by inflammation and possible irreversible damage to the blood vessel lumens. Despite generally being a diagnosis of exclusion, it may be a primary disease. However, it is normally caused by or associated with a number of other disorders or factors, including infections, autoimmune disorders, and allergy or hypersensitivity reaction to drugs, environmental irritants or toxins [1]. A common cutaneous manifestation includes necrotising blisters and lesions.

The ANCA-Associated Vasculitis (AAV) is a systemic autoimmune disorder and has been established as one of the most common causes for necrotising vasculitis of the small vessels, associated with cutaneous manifestation [2]. It is very rare, with a reported incidence of less than 20 new cases per million people every year [2], with around 150 cases in one million population [1,2]. Despite demonstrating paucity in complement and immunoglobulin deposits, which differentiate it from other autoimmune disorders

[3], its pathophysiology including the role of complement alternative pathway is still debatable and under great research interests [3,4].

Being a systemic disease, necrotising vasculitis belongs to a larger group manifesting as the vasculitic syndromes. These syndromes' spectrum ranges from a very modest presentation limited to the cutaneous system to the involvement of multiorgan systems which could be life threatening. The c-ANCA associated vasculitis, as present in the index case, affects the small and medium sized vessels and may cause granulomatosis and necrotising polyangiitis [2]. Involvement of almost all systems may occur, including the respiratory, nasal sinus, gastrointestinal, renal, urogenital, cutaneous and even ocular system. This represents a challenge in diagnosis and subsequent management, since clinical presentation from one system may feature predominantly than the others and may leads the attending doctors into misdiagnosis.

In this case, the obvious and aggressive appearance of the skin lesions led to the assumption of possibility for necrotising fasciitis causing multiorgan sepsis, since the latter is more common. However, a thorough analysis of the history and physical examination, combined with a high index of suspicion, made the diagnosis of necrotising fasciitis as least likely. With a contrasting pathogenesis, necrotising fasciitis is an aggressive soft tissue infection that rapidly spread along the fascial layer and subcutaneous tissue, and commonly caused by a polymicrobial infection in immunocompromised patients and monomicrobial in healthy individuals [5].

A few hints in the presentation of the patient led to the exclusion of this diagnosis in this case: rapid history of only one day- this is quite rare for necrotising fasciitis; premorbid history of the patient-necrotising fasciitis typically caused by infection affecting the immunocompromised patients especially the diabetic patients; history of recent consumption of unknown traditional medicine-a factor which was needed to be considered that may have triggered systemic disorder such as autoimmune diseases or hypersensitivity reactions; multiple limbs involvement for the cutaneous lesions-necrotising fasciitis typically confined to a single limb; and localisation of the cutaneous lesions-necrotising fasciitis progress rapidly, with the infection usually spread proximally or distally to the adjacent subcutaneous and fascial layers. The negative tissue culture from the probe test had also supported the unlikeliness of necrotising fasciitis. On another note, although the blood culture grew streptococcus, streptococcal infection usually presents with general scarlet rashes or erysipelas, rather than necrotising blisters [5]. However, either the streptococcal infection or the traditional medication consumed by the patient may have been the factor that triggered the exaggerated autoimmune responses in this patient.

The key that led to the correct diagnosis was of course the laboratory investigations. Despite their usefulness to detect infection, infective markers such as total white cell count, ESR and CRPC may also be elevated in other inflammatory inducing disorders. Serological biomarkers therefore play a major role- the level of serum C3 and C4 is very important in determining the presence of immune-complex diseases. Although both often decreased in these diseases, a low level of serum C3 combined with a normal level of C4 is suggestive of activation of complement alternative pathway, a demonstrable feature in AAV [3,6]. Immunofluorescence and Enzyme-Linked Immunosorbent Assay (ELISA) tests are then used to detect ANCAs. The type of ANCAs-c-ANCA, p-ANCA, and atypical ANCA-is normally differentiated based on the locality of pattern of the fluorescence occurring (perinuclear for p-ANCA and throughout cytoplasm for c-ANCA) [6]. Detection of other specific antibodies such as PR3 and MPO will further help to narrow down the diagnosis [6].

The gold standard diagnostic investigation for necrotising vasculitis is by skin biopsy. The best sample should be taken on a fresh lesion, suggested to be between 24 to 48 hours [7]. A pathognomonic finding is the presence of neutrophils infiltrating the lumen walls and undergoing karyorrhexis (leukocytoclasia), with the presence of nuclear debris [4,7]. The presence of fibrinoid necrosis is almost always constant [4], with additional features of endothelial swelling and erythrocytes extravasation [7]. As in this patient, the presence of granulomatous inflammation surrounding the lumens points towards granulamotosis with polyangiitis, a condition caused by c-ANCA associated vasculitis. In an older lesion, lymphocytes may feature predominantly instead of neutrophils [7]. The presence of eosinophils on the other hand may suggest drug induced necrotising vasculitis, instead of AAV [7].

The treatment of necrotising vasculitis depends heavily on its cause- if it is secondary to infection, drugs, irritants or environmental factors, elimination of cause may improve the patient condition rapidly. In immune-complex vasculitis, medical therapy is the mainstay of treatment, with systemic corticosteroid (such as prednisone and hydrocortisone) is the main drug used. Fibrinolytics (such as heparin), CD20 blockers (such as rituximab) and TNF-alpha blockers (such as adalimumab, infliximab and etanercept) are also being used to treat this type of vasculitis, in addition to immunosuppressing drugs such as cyclophosphamide and azathioprine [1]. For AAV, a specific recommendation has been proposed with the drugs to be commence according to the stage of the disease (acute, major relapse or remission) and severity of organ or life threatening condition [2,8]. The duration of the drugs, especially the corticosteroid, also varies from 3 months to a lifelong maintenance dosage [1,2,8].

Unlike in necrotising vasculitis, early and aggressive surgical debridement combined with empirical antibiotics is the appropriate management for necrotising fasciitis [5]. In this case, avoidance of aggressive surgical debridement and prioritisation of medical therapy helped our patient to achieve optimal functional outcomes. On the other hand, a low C3 level is found to be associated with poor prognosis in AAV, especially in regards to the renal failure [3]. This did not happen to our patient, who gradually became completely independent from haemodialysis and eventually enjoyed a good quality of life with his recovery.

CONCLUSION(S)

Despite of its rarity, any abnormal skin lesion may be a subtle presentation of necrotising cutaneous vasculitis. A high index of suspicion through a multidisciplinary approach, coupled with meticulous investigative process including serological biomarkers and skin biopsy, helps to avoid misdiagnosis which may be detrimental to the patient.

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