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A Possible Cephalexin-Induced Cutaneous Vasculitis

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Introduction

Cutaneous Vasculitis (CV) is a condition that presents with inflammation in the subcutaneous tissue and dermis. CV is most commonly found to affect the skin but rarely can also cause a systemic vasculitic syndrome that manifests with end-organ involvement [1].

The etiology of CV often is unknown, but strong associations have been linked with inflammatory disorders, connective tissue disorders, systemic vasculitis, infections, drug-induced vasculitis, and neoplasms. Infectious etiologies can include Staphylococcus Aureus, Chlamydia, Neisseria, and Mycobacterium. In addition, chronic infections with hepatitis B, hepatitis C, and syphilis have also been related to CV. In regards to drug-induced vasculitis, the following medications have been associated with CV: beta-lactams, erythromycin, clindamycin, vancomycin, sulfonamides, furosemide, allopurinol, NSAIDs, amiodarone, phenytoin, TNF-alpha inhibitors, and warfarin. Onset is usually 7 to 21 days after the drug initiation [2].

CV presents with the following histopathologic changes: evidence of neutrophilic infiltration within and around the vessel wall with signs of activation, death, and degranulation of neutrophils, and fibrinoid necrosis [3]. The hallmark sign of CV is palpable purpura over the lower extremities but it can appear in any area. Less common signs are urticarial plaques, vesicles, bullae, and pustules. Of note, extracutaneous involvement occurs in patients at a rate of 30 percent [4].

The diagnostic criteria of CV must include a detailed history, complete physical exam, and confirmatory laboratory testing that should specifically include antinuclear antibody and antineutrophil cytoplasmic antibody testing, hepatitis B and C serologies, complement levels, immunoglobulins, blood count, serum creatinine, liver function tests, urinalysis since early renal involvement can be silent, radiographic imaging, and biopsy [5].

The pathologic mechanism of CV is caused by the deposition of immune complexes at the vessel wall causing an inflammatory reaction related to granulocytes. Corticosteroids help to suppress the immune reaction; however, the effects of medication treatment are temporary. The best treatment option is to prevent the formation of immune complexes by eliminating the antigen (such as drugs or acute/chronic infection of tonsils/pharynx with group A streptococci, hepatitis B, or C) [6].

Keywords: Cephalexin; Small-vessel; Cutaneous; Vasculitis; Palpable purpura

Case Presentation

The patient is a 62-year-old male who was readmitted back to the hospital after treatment for a right foot abscess with the new complaint of bilateral lower extremity rash. The patient has a past medical history significant for end-stage renal disease caused by diabetic nephropathy, hypertension, coronary artery disease, diabetes mellitus type 2, and a history of left great toe amputation secondary to a diabetic foot ulcer. The patient had been recently admitted with a right foot blister and cellulitis. During the course of hospitalization, infectious disease was consulted and the patient received cefazolin 1 g IV for one dose. Foot x-ray did not show lytic lesions, osteopenia, periosteal thickening, loss of trabecular architecture, or new bone apposition consistent for osteomyelitis. MRI and CT were not done as the initial acute phase reactants were within the normal range. The patient underwent incision and drainage by podiatry. Wound culture grew Staphylococcus aureus. He was subsequently discharged home on cephalexin 250 mg t.i.d for 10 more days.

He later presented to the hospital 10 days after discharge due to bilateral purpuric and bullous lesions localized on the lower extremities after starting to take the medication. He stated that the symptoms began towards the end of the cephalexin course. The most likely etiology of the cutaneous vasculitis was cephalexin use as it best fits the post-7-day course described in the literature (Figure 1). On admission, his vitals were within normal range. Skin examination revealed bilateral purpuric non-blanching papules localized on the anterior and lateral aspects of the patient's lower extremities (Figure 2, Figure 3). Lesions were not tender to palpation and no mucosal or palmar involvement was

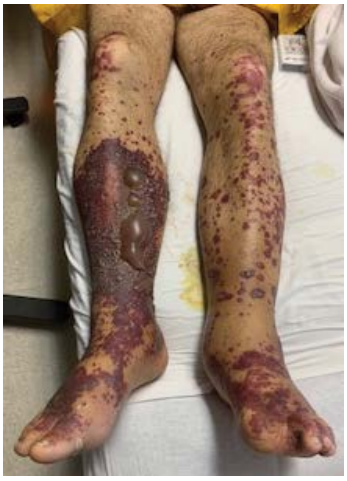

Figure 1: Palpable purpuric and bullous lesions located mainly on the lower extremities.

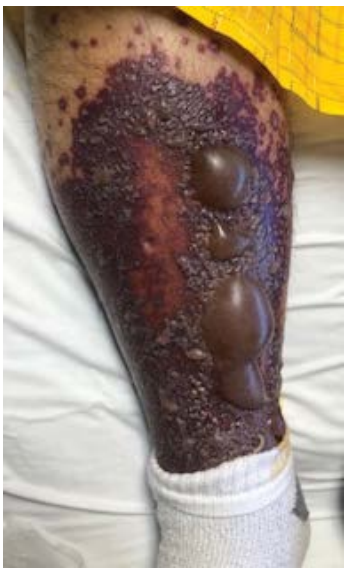

Figure 2: Confluent, palpable erythematous non-blanching purpura and bullous lesions mainly seen on the right lower extremity.

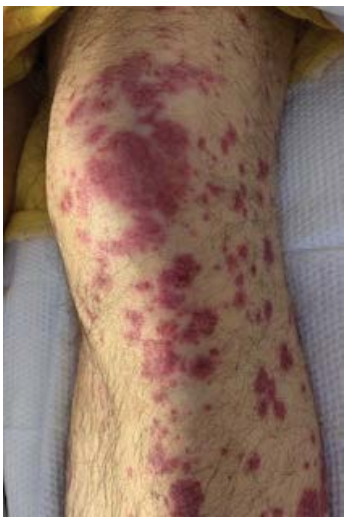

Figure 3: Multiple palpable round-ovular lesions on the lateral and anterior aspect of the left lower extremity.

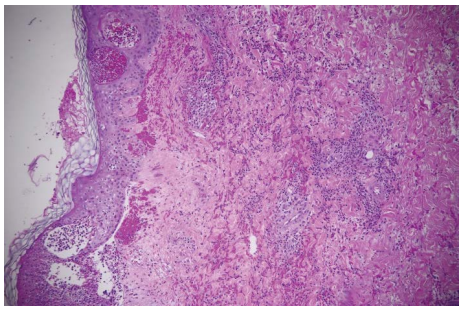

Figure 4: H&E, original magnification x100. Area of heavy neutrophilic infiltrate closer to the surface of the skin and there are foci of perivascular inflammation.

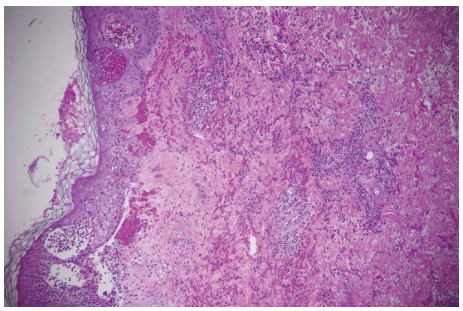

Figure 5: H&E, original magnification x400. Vessels with neutrophilic infiltrate and additional neutrophils in the stroma.

observed. The patient denied any other acute complaints such as fever, chills, abdominal pain, arthralgias, paresthesia, or itching. He did not reveal any known drug allergies in the past. He had an elevated CRP on admission, 6.6 mg/dl (normal 0-0.9 mg/dl), but no other abnormal findings in red blood cell count, white blood cell count, kidney or liver function was observed. Urinalysis did not reveal proteinuria or hematuria.

Due to the temporal relationship between cephalexin initiation and the development of skin findings, the diagnosis of cephalexin-induced CV was suspected. Cephalexin was discontinued on admission and the patient was started on methylprednisolone 60 mg IV t.i.d.

To confirm the suspected diagnosis of CV, a biopsy of the skin with direct immunofluorescence was performed. It showed severe Cutaneous Vasculitis. The lesion was characterized by a pronounced perivascular infiltration of neutrophils with a small number of eosinophils and other cells and focal infiltration of the vascular wall. There was no significant linear or granular staining at the dermal-epidermal junction for IgG, IgA, IgM, C3, or fibrinogen (Figure 4). The presence of large subepidermal and intradermal clusters of neutrophils are consistent with a severe form of Cutaneous Vasculitis referred to as pustular vasculitis (Figure 5).

During the patient's hospitalization, an extensive serological screening was ordered to recognize any possible immunologic etiology. Further testing included: acute hepatitis panel, cryoglobulins, rheumatoid factor, ANA, c-ANCA, p-ANCA, anti-Ro Ab, anti-La Ab, anti-Smith Ab, anti-RNP Ab, anti-dsDNA Ab, C3, and C3 with total complement. The patient had negative results for all. A chest x-ray did not show any signs of malignancy. Prior MRI of the abdomen and pelvis did not reveal any acute findings. He had a non-reactive PPD upon follow-up in the outpatient setting. Neisseria and Chlamydia were not checked as sexual history did not give rise to any risk factors.

After several days of hospitalization, purpuric lesions on bilateral extremities improved after treatment. He was discharged hemodynamically stable.

Discussion

Beta-lactams, including cephalexin, are usually safe and well-tolerated but in rare cases are associated with many adverse drug reactions. This case report shows a patient that developed CV after taking cephalexin. This patient had the most common manifestation of small vessel vasculitis that is palpable purpura. He did not have any extracutaneous manifestations, therefore it was a localized CV. Most of the cases are idiopathic, however, some CV cases have been found to be drug-induced. Cephalexin was the only recently added medication to our patient. Although CV is a rare condition, it has been reported with the use of some medications including clozapine, quetiapine, and rivaroxaban, among others. A review of the literature through PubMed did not show an association between CV and Cephalexin in previous articles.

According to the Naranjo Adverse Drug Reaction Probability Scale, characteristics of CV include purpura and maculopapular rash, adult age of onset after the use of a drug, and biopsy of the lesion showing neutrophils around a blood vessel. Our patient met all these criteria. All serological testing completed to identify an immunologic etiology was found to be negative. He gradually improved after stopping the medication and being managed with systemic steroids. Even if there is a very low possibility, CV should be considered while prescribing cephalexin and it is important to be aware of this uncommon side effect.

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