Cutaneous Vasculitis Associated with Fluoroquinolones

G. Maunz, T. Conzett, W. Zimmerli

Abstract
Cutaneous vasculitis is a clinical entity with a broad differential diagnosis, including an adverse drug reaction. It is defined as inflammation of skin blood vessel walls. During a 7-year-period, we observed three patients who developed isolated cutaneous vasculitis during antibiotic therapy of bacterial infection. All were treated with a fluoroquinolone (ciprofloxacin or levofloxacin) combined with rifampin (two cases) or flucloxacillin (three cases), respectively. In all three cases the lesions gradually resolved after treatment with the inciting fluoroquinolone had been stopped. In one patient, leukocytoclastic small-vessel vasculitis was histologically confirmed. Fluoroquinolone-associated cutaneous vasculitis consists of an isolated self-limiting disorder that is part of a systemic vasculitis, or even life-threatening disease. Clinicians should be aware of this serious adverse event because any continuation of treatment may be fatal.

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Introduction

Cutaneous vasculitis is defined as inflammation of the skin blood vessels [1]. Histologically, the most common cutaneous manifestation of this clinical entity is leukocytoclastic vasculitis, which preferentially affects small vessels of the lower extremities and is clinically characterized by palpable purpuric lesions, sometimes with slight focal necrosis and ulceration [2]. No obvious triggering event has been detected to date in primary vasculitis; in contrast, the etiology of secondary vasculitis is known [3] and includes inflammatory reaction to drugs, infection, neoplasia, or autoimmune disease. Isolated cutaneous leukocytoclastic vasculitis is often associated with a drug hypersensitivity response, and the clinical symptoms improve when the drug is stopped [4]. Drugs that have been implicated in the hypersensitivity response include penicillins, aminopenicillins, sulfonamide-based drugs (including antibacterial sulfonamides as well as most loop- and thiazide-type diuretics), quinolones, allopurinol, and propylthiouracil [1]. Hypersensitivity vasculitis is commonly associated with circulating immune complexes. The drugs act as haptens, stimulating an immune response, followed by the formation of circulating immune complexes that are deposited in postcapillary venules and arterioles, inducing inflammation [1].

Case Reports

Case 1

A 68-year-old man with a hematogenous total knee arthroplasty-associated infection due to *Staphylococcus aureus* was treated with debridement and iv-flucloxacillin. Two weeks later, antibiotics were switched to oral ciprofloxacin plus rifampin. After 7 days, an erythematous palpable purpuric rash appeared on both legs. This exanthema was interpreted as a manifestation of an uncontrolled infection. One week later, a dermatologist, who was asked to consult with the patient due to progressing necrotic skin lesions, clinically diagnosed drug-induced vasculitis and stopped treatment with both antibiotics. Following continuation of the treatment with flucloxacillin alone, and later with fusidic acid plus rifampin, all lesions gradually healed.

Case 2

A 74-year-old man with a vascular prosthesis-associated infection due to *S. aureus* was treated with iv-flucloxacillin. Two weeks later, ciprofloxacin was added because of nosocomial urinary tract infection due to *Klebsiella pneumoniae*. After 8 days, hemorrhagic lesions and palpable purpura appeared (Figure 1). This exanthema was diagnosed as Janeway lesions, and endocarditis was considered as differential diagnosis. However, the Infectious Disease consultant diagnosed drug hypersensitivity based on the presence of only two minor Duke criteria and because the consultant had been primed by the former case. Therefore, ciprofloxacin was immediately stopped, and the lesions gradually disappeared within 1 week despite continuous flucloxacillin therapy.

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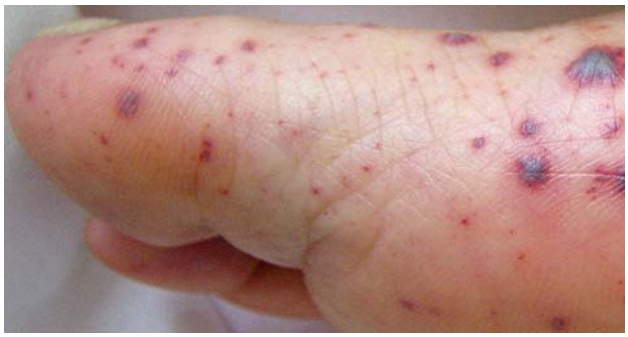

Figure 1. Case number 2. Acute appearance of palpable purpura after 3 weeks of therapy of *S. aureus* sepsis with flucloxacillin, and after 1 week treatment of an urinary tract infection with ciprofloxacin.

Case 3

A 65-year-old man suffered from a cervical hematogenous epidural abscess after iv-catheter-associated sepsis due to *S. aureus*. After neurosurgical débridement, he was treated with iv-flucloxacillin for 2 weeks and then switched to oral levofloxacin plus rifampin. Three days later, palpable purpura appeared. Leukocytoclastic small-vessel vasculitis was histologically confirmed by means of a punch biopsy (Figure 2). After the levofloxacin plus rifampicin drug therapy was stopped and the patient switched back to flucloxacillin alone, the skin lesions rapidly disappeared. Rifampicin was later reintroduced together with fusidic acid because no case of cutaneous vasculitis due to rifampin has been described to date. After an overall drug treatment of 7 weeks, therapy was stopped without reappearance of skin vasculitis.

Discussion

All three patients described here had clinically and/or histologically confirmed cutaneous small-vessel vasculitis [5] without antineutrophil cytoplasmatic antibodies (ANCA). None of the patients showed evidence of glomerulonephritis or other systemic involvement. In each of these patients, the appearance and disappearance strictly correlated with ciprofloxacin or levofloxacin therapy.

Drug-induced immune complex vasculitis, also denoted hypersensitivity vasculitis, is a small-vessel vasculitis involving postcapillary venules and arterioles. It is a common clinical feature of a severe cutaneous reaction induced by drugs [2] and has the clinical hallmarks of palpable purpura and/or petechiae. Diagnosis must be considered in the case of typical clinical findings and a history of a new therapy with a drug known to potentially cause hypersensitivity vasculitis. Skin biopsy shows a leukocytoclastic vasculitis (Figure 2), i.e., intense infiltration of inflammatory cells, primarily polymorphonuclear leukocytes, and fragments of degenerated leukocyte nuclei (''nuclear dust''). The immune complexes are deposited in tissue, thereby causing vasculitis [1] through the narrowing and occlusion of the vessel lumen and by necrosis of the wall. Drugs implicated in hypersensitivity vasculitis include penicillins, aminopenicillins, sulfonamide-based drugs (including antibacterial sulfonamides

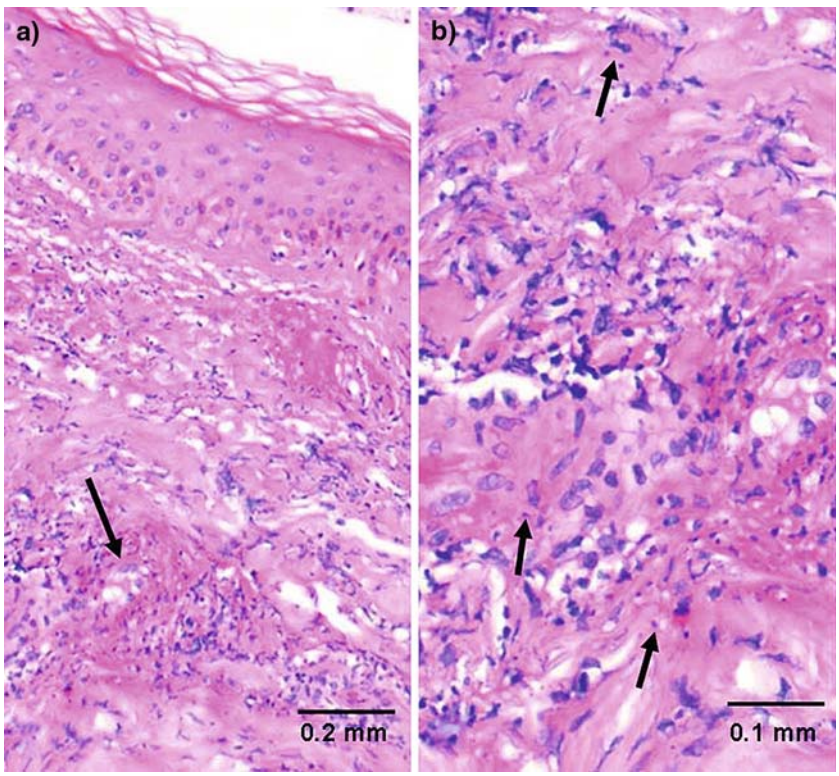

Figure 2. Case number 3. Section from a punch biopsy of skin lesions (palpable purpura) which appeared 3 days after the antibiotic therapy of the patient had been switched from flucloxacillin to levofloxacin plus rifampicin (hematoxylin + eosin stain; magnification ×200 left, ×400 right). a) Fibrinoid type necrosis (arrow), b) Fragmented neutrophils (arrow) (Courtesy of Prof. G. Cathomas, Kantonales Institut für Pathologie, Liestal).

as well as most loop- and thiazide-type diuretics), quinolones, allopurinol, and propylthiouracil [2]. Some drugs act as haptens, conjugating to serum proteins and mediating the formation of immune complexes (e.g., penicillins). Other drugs, such as foreign proteins, including streptokinase, cause cutaneous vasculitis by the formation of immune complexes [6]. In addition, some drugs appear to cause vasculitis by inducing ANCA (e.g., propylthiouracil, anti-tumor-necrosis factor-α), although a cause-and-effect relation has not been proven [7]. Vasculitis usually starts 7–10 days after antigen exposure, by which time sufficient immune complexes have been produced [1]. However, the latent period may be as short as 2–7 days (case no. 3) with a secondary antigen exposure, or longer than 2 weeks with a long-acting drug, such as benzathine penicillin [8]. The fact that a patient has been receiving a drug for an extended time does not exclude that drug from consideration because drug hypersensitivity is not time- or dose-dependent [9]. Discontinuation of the inciting drug should result in the prompt resolution of signs within days to a few weeks.

A special form of non-ANCA vasculitis is Henoch–Schönlein purpura. It is clinically characterized by purpura, abdominal pain (gut vasculitis), nephritis (renal vasculitis), and arthralgia/arthritis (immune complex synovitis). Immune histochemistry shows vascular deposition of immunoglobulin (Ig)A-dominant immune complexes in small vessels. It is most frequent in childhood, with a peak incidence at age 5 years. This disease often begins after an upper respiratory tract infection, and it is not correlated with drug therapy [10].

Cutaneous vasculitis has also been observed during infections, such as endocarditis, bacteremia due to meningococci and gonococci, and chronic hepatitis C as well as other chronic infections. The mechanism of infection-associated vasculitis is also vascular inflammation due to the formation of local immune complexes. Although our three patients had severe *S. aureus* infection, it was not the cause of their cutaneous vasculitis because of the strict correlation between starting and stopping fluoroquinolone therapy and the manifestation and (gradual) disappearance of symptoms, respectively.

No association with ANCA has been described in quinolone-induced vasculitis, unlike in Wegener's granulomatosis, Churg–Strauss syndrome, or microscopic polyangiitis.

Several cases of cutaneous and/or renal vasculitis due to ciprofloxacin, ofloxacin, and levofloxacin drug therapy have been reported [11–20]. In the published Swiss drug information sheet (Swiss Drug Compendium, Documed, Basel), cutaneous vasculitis is mentioned as adverse events of ciprofloxacin and ofloxacin, but not of levofloxacin. Whether it is a class effect of fluoroquinolones is unknown. According to Pubmed, with the exception of the three patients reported here, there have been no cases of cutaneous vasculitis as an adverse event to other fluoroquinolones. In view of our three cases within 7 years (13,700 hospitalized patients/year), cutaneous vasculitis associated with ciprofloxacin, ofloxacin, or levofloxacin is not a very rare event. Skin lesions may be misinterpreted as a sign of infection. Therefore, each clinician should be aware of quinolone-associated hypersensitivity vasculitis, since any continuation of therapy may be fatal [15].

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