

Etodolac-induced hypersensitivity vasculitis with digital gangrene

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ABSTRACT Non steroidal anti-inflammatory drugs are one of the most commonly prescribed drugs and can result in hypersensitivity vasculitis, sometimes with grave consequences. We report a case of a female who developed digital gangrene following the use of etodolac.

KEYWORDS Etodolac, digital gangrene, non steroidal anti-inflammatory drugs, hypersensitivity vasculitis, leukocytoclastic vasculitis

LIST OF ABBREVIATIONS Antinuclear antibodies (ANA), cerebrospinal fluid (CSF), computerised tomography (CT), non steroidal anti-inflammatory drug (NSAID), red blood cell (RBC), white blood cell count (WCC)

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CASE REPORT

A 60-year-old female was admitted to hospital with three days' history of low grade fever, generalised skin rash and discolouration of her fingers and toes, and one day's history of altered level of consciousness. Her medical record revealed that she had been suffering from seronegative polyarthritis for the previous five years. She had been taking various analgesics when required, but never used any disease-modifying drug. She had two discrete episodes of allergic reactions to ibuprofen characterised by generalised urticaria and swelling of lips. There was no history of allergy to any other drug. Three days prior to her admission, she took two tablets of etodolac, brought by her relative from abroad. She did not take any other medicine concomitantly. Personal and family history contributed nothing.

On admission, she was febrile, drowsy and irritable. There was widespread non-blanching erythematous maculopapular rash and bluish-black patches of skin necrosis mainly on her nose, arms and legs. Many of her digits were gangrenous at their distal ends (see Figures 1 and 2). There were ulcers in her oral cavity. She was in respiratory distress with stridor and respiratory rate of 24 breaths per minute. There was tachycardia but her blood pressure was normal. Her neck was stiff but Kerning's sign was absent. The rest of her clinical examination was unremarkable. Investigations revealed mild anaemia (haemoglobin 9.7 G/dl), thrombocytopenia (platelets 79×10^9) and neutrophil leukocytosis (WCC 10.1×10^9 with 82% neutrophils). Reticulocyte count was normal and fragmented RBCs were not detected. Her

renal functions were deranged with a blood urea of 19.6 mmol/L and creatinine of 115 μ mol/L. Blood glucose, sodium, potassium and bicarbonate were normal. Serum alanine aminotransferase was slightly elevated (61 u/l) but serum bilirubin, serum aspartate aminotransferase, alkaline phosphatase, creatine kinase, prothombin time and partial thromboplastin time were within the normal range. Serum lactic dehydrogenase was 1,040 U/L, serum fibrin degradation products >500 but $<1,000$ U/L and serum fibrinogen 190 mg/dl. Her CSF revealed protein, 96 mg/dl, glucose, 36 mg/dl and white blood cells, 42×10^6 /L (mostly neutrophils). No organism was detected on Gram stain/culture of CSF, which was also negative for meningococcal antigen. Samples from necrotic skin patches did not reveal meningococci on Gram stain. Her electrocardiogram, chest X-ray, urine, CT brain scan, abdominal ultrasound, and arterial blood gases were all normal. Antinuclear antibodies, rheumatoid factor, Coomb test, antineutrophil cytoplasmic antibodies (cANCA & pANCA), and anti-double-stranded-DNA antibodies were also negative. Antithrombin III, protein C & S levels were normal. Serum complements (C3 & C4) were within normal limits but C-reactive protein was slightly elevated (12 mg/L). Her skin biopsy showed peripheral neutrophilic infiltration with minimal necrosis and extravasations of RBCs and was consistent with leukocytoclastic vasculitis. She was managed with parenteral antibiotics, steroids, anticoagulants and other supportive measures. Over the next three days, her fever settled and she became fully conscious and communicative. Her haematological, renal and hepatic profiles also improved. Her skin rash resolved and necrotic areas of skin started shedding off. Digital



FIGURE 1 Digital gangrene and necrotic skin patches.

gangrene did not progress further. She was advised to avoid NSAIDs, particularly etodolac and ibuprofen, in the future, and was transferred to another hospital under the care of a vascular surgeon who carried out distal amputation of all the involved fingers and toes. Following successful surgery, she was discharged. However, six weeks later, she developed an infection in one of her amputated hands and died due to severe sepsis.

DISCUSSION

Hypersensitivity vasculitis can be caused by many drugs, particularly penicillins, cephalosporins, sulfonamides, phenytoin, allopurinol, loop and thiazide diuretics.¹ Recently, NSAIDs have been ranked second only to antibiotics in causation of skin reactions.² Among NSAIDs, piroxicam, tenoxicam, diflunisal, sulindac, and etodolac had the highest risk, while the relative risk with diclofenac and ibuprofen is low.³ In 1996, Lie and Dixit,⁴ described a case of hypersensitivity vasculitis of the temporal artery induced by etodolac, and in 2001, Davidson *et al.*⁵ described a case of ibuprofen-induced leukocytoclastic vasculitis.

Hypersensitivity vasculitis due to drugs can be identified on the basis of five defining characteristics:⁶ age > 16 years, use of a possible offending drug in temporal relation to the symptoms, palpable purpura, maculopapular rash, and biopsy of a skin lesion showing neutrophils around an arteriole or venule. In this case, there was a temporal relation between the onset of clinical deterioration and



FIGURE 2 Digital gangrene and necrotic skin patches in lower limb.

the use of a known offending agent, so the diagnosis of 'drug-induced (etodolac) hypersensitivity vasculitis' was made. Her previous allergy to ibuprofen made her vulnerable to etodolac as it is known that ibuprofen and etodolac share similar side effect profile.⁷ Thrombotic thrombocytopenic purpura is unlikely as her bilirubin and reticulocyte count were normal and fragmented RBCs were not detected. Elevated proteins and cells in CSF were not high enough to support the diagnosis of meningococcal meningitis. Moreover, quick clinical recovery and absence of meningococci and meningococcal antigens in CSF are also against this diagnosis. Vasculitis associated with rheumatoid arthritis and other forms of vasculitides are also unlikely in view of negative rheumatoid factor, ANA and ANCA with normal complement levels. Non steroidal anti-inflammatory drugs can produce symptoms and signs of meningeal irritation with CSF pleocytosis, increased protein, and low to normal glucose.⁸ This case underscores the fact that NSAIDs can lead to hypersensitivity vasculitis which can sometime be severe enough to cause digital gangrene necessitating amputation. It also implicates etodolac as an offending agent for hypersensitivity vasculitis and highlights its cross reactivity with ibuprofen. We believe that it is the first ever case report of etodolac/NSAID associated hypersensitivity vasculitis leading to digital gangrene from Pakistan.

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