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Case Report

Proteinase 3-antineutrophil cytoplasmic antibody positive necrotizing vasculitis induced by ciprofloxacin

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ABSTRACT

Granulomatosis with polyangiitis (Wegener's), microscopic polyangitis, and eosinophilic granulomatosis with polyangiitis are commonly grouped together as antineutrophil cytoplasmic antibody (ANCA)-positive vasculitides. Many drugs and infections can induce serologic positivity for ANCA, while a few can precipitate overt ANCA-positive vasculitis. Although fluoroquinolones have been reported to cause ANCA-negative leukocytoclastic vasculitis (LCV), fluoroquinolones are not known to induce proteinase 3-ANCA (PR3-ANCA)-positive vasculitis. Here, we present the case of a middle-aged man who developed severe headache, purpura on legs and numbness in hands and feet after taking ofloxacin for 5 days. Subsequently, he was diagnosed with ANCA-negative LCV and treated with steroids and immunosuppressants. Thirteen years later, he inadvertently received intravenous ciprofloxacin and developed severe headache and epistaxis. Serologic testing at that time revealed elevated titers of PR3-ANCA. Biopsy of nasal septum revealed a mixed mononuclear and polymorphonuclear infiltrate without evidence of granuloma formation. He was treated with steroids and immunosuppressive therapy. Over the next several years, he remained stable with residual hearing loss and nasal septal deformity. This case provides the first evidence for a PR3-ANCA-positive necrotizing vasculitis induced by ciprofloxacin.

Keywords: Granulomatosis with polyangiitis, ANCA, Associated vasculitis, Cutaneous, LCV, Wegener's granulomatosis

INTRODUCTION

Granulomatosis with polyangiitis (Wegener's), microscopic polyangitis, and eosinophilic granulomatosis with polyangiitis are commonly grouped together as antineutrophil cytoplasmic antibody (ANCA)-positive vasculitides. Many drugs and infections can induce serologic positivity for ANCA, while a few can precipitate overt ANCA-positive vasculitis.[1] Although ciprofloxacin can cause ANCA-negative leukocytoclastic vasculitis (LCV), fluoroquinolones are not known to induce proteinase 3-ANCA (PR3-ANCA)-positive vasculitis. Here, we present the case of a middle-aged man who developed PR3-ANCA-positive vasculitis after receiving ciprofloxacin.[2]

CASE REPORT

In 1995, a 32-year-old man presented with a 1-day history of severe headache and rash on his legs. He had completed a 5-day course of ofloxacin (400 mg×2/d) 1 day prior to presentation for an upper respiratory tract

infection. He reported numbness and loss of sensation in both hands and feet. On examination, he was febrile (temperature of 38.3°C; 101°F), but, his ENT examination was unremarkable. Palpable purpuras were noted over his left leg along with reduced sensation to pin-prick over the plantar surface of left foot. Laboratory investigations were notable for neutrophilic leukocytosis, positive anti-nuclear antibody (1:160), negative rheumatoid factor and normal ANCA levels. Punch biopsy of a skin lesion over the left medial malleolus revealed histopathologic features of LCV. Patient was prescribed an oral course of prednisolone (1 mg/kg) along with cyclophosphamide (pulse therapy) to which he responded well.

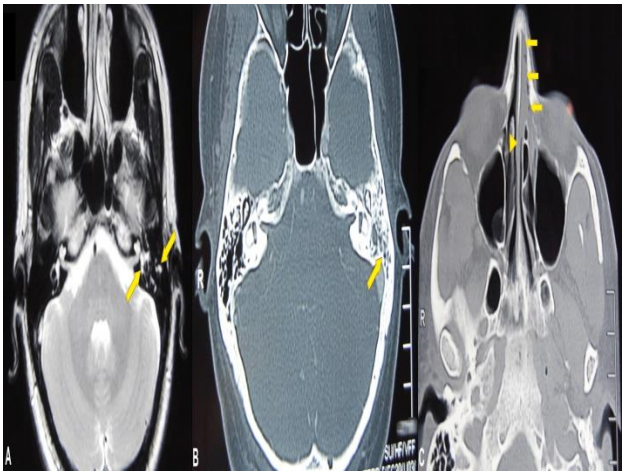

Figure 1: (A) Axial view of T2-weighted magnetic resonance image demonstrating the presence of fluid within left middle ear and mastoid air cells (arrows); (B, C) axial view of computed tomography showing; (B) opacification of mastoid air cells (arrow) and; (C) a soft-tissue density (arrows) within the nasal cavity causing erosion of nasal septum (arrowhead).

Thirteen years later, patient presented to the emergency department with blood-stained stools and was diagnosed with dysentery. Inadvertently, he received a single dose of intravenous ciprofloxacin (400 mg) at this time. The following day he experienced severe headache, one episode of epistaxis and generalized weakness. There were no cutaneous eruptions or numbness of hands and feet at that time. He was evaluated in the otolaryngology clinic and prescribed analgesics and decongestants. However, his condition worsened further. MRI brain was performed, which showed fluid within mastoid air cells and middle ear [Figure 1(A)] along with a soft-tissue density within nasal cavity. CT paranasal sinuses was also ordered, which showed an infiltrative, soft-tissue density within the nasal cavity along with erosion of nasal septum [Figure 1(B) and 1(C)]. Laboratory investigations at this time were notable for neutrophilic leukocytosis, elevated liver enzymes, normal serum creatinine and positive ANCA (classic immunofluorescence pattern) directed against proteinase-3. A nasal septal biopsy showed an admixture of mononuclear and polymorphonuclear infiltrate without any evidence of granuloma formation. Patient was treated with intravenous methylprednisolone (1 g/d×3) followed by an oral taper of prednisolone and immunosuppressive therapy. Over the next several years, patient remained stable with residual left-sided conductive hearing loss and nasal septal deformity.

DISCUSSION

In a comprehensive review of drug-induced rheumatologic disorders published, Bukhari identified four groups of drugs that commonly induce vasculitic disorders; these groups included anti-thyroid drugs, anti-tumor necrosis factor (TNF) medications, levamisole-adulterated cocaine and new small molecules.[1] The spectrum of drug-induced vasculitis ranges from ANCA-negative vasculitis to ANCA-positive LCV to necrotizing neutrophilic dermatosis with positive antiphospholipid antibodies.[3-5] Drug-induced ANCA-positive vasculitis is often due to antibodies directed against myeloperoxidase, cathepsin G, lactoferrin or bacterial permeability increasing protein.[6]

Drug-induced necrotizing vasculitis due to PR3-ANCA has been rarely reported. Only a few drugs (propylthiouracil, methimazole, hydralazine, minocycline and levamisole-adulterated cocaine) have been previously reported to cause this severe vasculitic disorder.[7-9] Fluoroquinolones are a generally well-tolerated class of drugs. In the literature, only a few cases have been reported hitherto regarding the development of fluroquinolone-induced vasculitis.[6] Storsley and Geldenhuys reported a rare case of ANCA-negative LCV induced by ciprofloxacin.[10] To the best of our knowledge, the present case provides the first evidence for a PR3-ANCA-positive necrotizing vasculitis induced by ciprofloxacin.

The strength of causal relationship of a drug with a probable adverse reaction is often judged by the Naranjo adverse drug reaction (ADR) probability scale. Based on responses to 10 items, a score is calculated regarding the likelihood of an ADR. Keeping the current case in perspective, a score of 8 can be calculated, which is consistent with a probable ADR. This score, when read in conjunction with previous reports of drug-induced vasculitis, provide strong evidence for a ciprofloxacin-induced PR3-ANCA-positive vasculitic disorder.

CONCLUSION

Although rare, ciprofloxacin may induce a proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA)-positive necrotizing vasculitis. Based on the evidence provided in this case, it would be prudent to avoid fluoroquinolones (whenever possible) in patients with a history of antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis.

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