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Acute immuno-allergic interstitial nephritis caused by fluindione

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Key words

fluindione – acute interstitial nephritis – kidney biopsy – corticosteroids

Abstract. Fluindione is a vitamin K antagonist that is commonly prescribed for the treatment of cardiovascular disease and venous thromboembolism in France. Bleeding is the most common side effect of fluindione, whereas hypersensitivity reactions are rare. We describe here a patient with acute immuno-allergic interstitial nephritis caused by fluindione. Initial symptoms included fever, eosinophilia, low albuminuria, microscopic hematuria, eosinophiluria and acute renal failure. Kidney biopsy showed severe interstitial nephritis with interstitial edema, inflammatory infiltrates and tubulorrhexis. Fluindione withdrawal and corticosteroid treatment resulted in rapid recovery of renal function. A review of the literature revealed a very low incidence of fluindione-induced interstitial nephritis, with variable renal and extra-renal signs. Early recognition of this rare complication may prevent the development of severe chronic renal injury.

Introduction

Oral anticoagulant therapy is commonly used for the treatment and prevention of thrombosis in various conditions including venous thromboembolism, peripheral vascular disease, atrial fibrillation and ischemic and valvular heart diseases. Among the vitamin K antagonist drugs, fluindione is more frequently used than warfarin or coumarin in France. Acute interstitial nephritis (AIN) is an uncommon renal disorder, accounting for 2 – 3% of episodes of acute renal failure [Buysen et al. 1990, Cameron et al. 1988]. Renal failure characterized by cellular interstitial infiltrates may be secondary to various infections or systemic diseases such as sarcoidosis, systemic lupus erythematosus and Sjogren's syndrome, or lymphoproliferative disorders. However, drugs, namely antibiotics

and non-steroidal anti-inflammatory agents (NSAIDs), are now the most common cause of AIN, the frequency of which is increasing [Davidson et al. 1998].

Fluindione has been reported in very few cases as a cause of AIN [Grimaldi et al. 2005]. We describe a patient with biopsy-proven fluindione-induced AIN and review the pertinent literature.

Case report

A 70-year-old man was admitted because of fever, malaise, abdominal pain and acute renal failure after treatment for a right sural vein thrombosis with fluindione, 3 weeks before. The patient had no history of allergic diathesis, renal disease, diabetes mellitus or hypertension and no current or recent medication, except for fluindione. Serum creatinine level was normal 10 days prior to admission (1 mg/dl). On physical examination, heart, lungs, skin, abdomen and lymph nodes were unremarkable. Funduscopic examination was normal. Temperature was 38 °C, blood pressure 120/60 mmHg, heart rate 65 bpm and daily urine output 1.2 l/24 h. Laboratory data on admission were as follows: proteinuria 0.3 g/day, serum creatinine 4.6 mg/dl, total protein 6.5 g/dl, albumin 3.1 g/dl, urea 94 mg/dl, potassium 4.6 mEq/l, sodium 135 mEq/l, uric acid 5.8 mg/dl, calcium 8 mg/dl, phosphorus 2.9 mg/dl, aspartate aminotransferase 40 UI/l, alanine aminotransferase 50 UI/l, alkaline phosphatase 154 UI/l and CRP 11 mg/dl. Full blood count was normal, except for mild anemia (hemoglobin 11.9 g/dl) and eosinophilia ($1.6 \times 10^9/l$). Phase-contrast microscopy urinalysis showed altered eosinophils, lymphocytes and mild microscopic hematuria. Ab-

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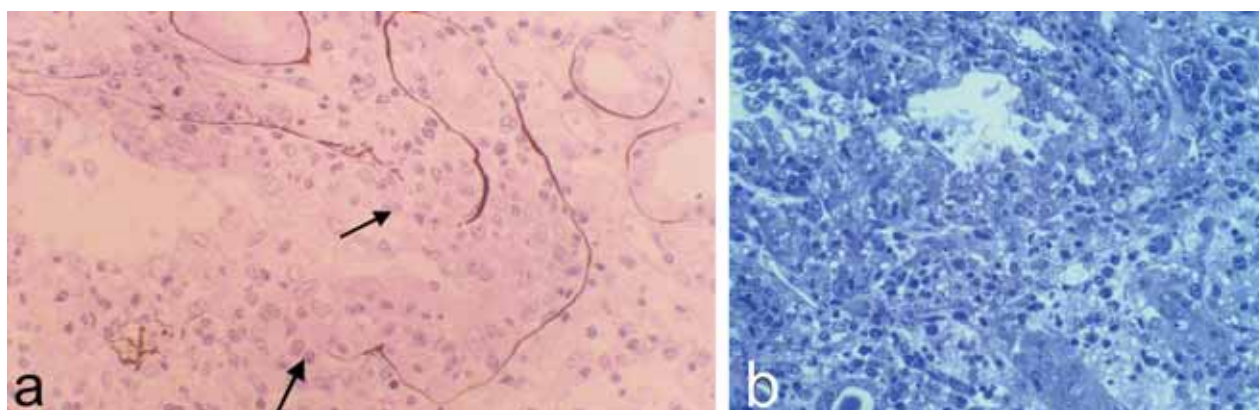


Figure 1. Kidney biopsy, light microscopy: a (silver staining, original magnification $\times 400$): interstitial edema with numerous inflammatory cells and tubulorrhexis with tubular basement membrane disruption (arrow). b (toluidine-blue staining, original magnification $\times 200$): diffuse interstitial inflammatory infiltrate by lymphocytes, neutrophils, eosinophils and plasma cells.

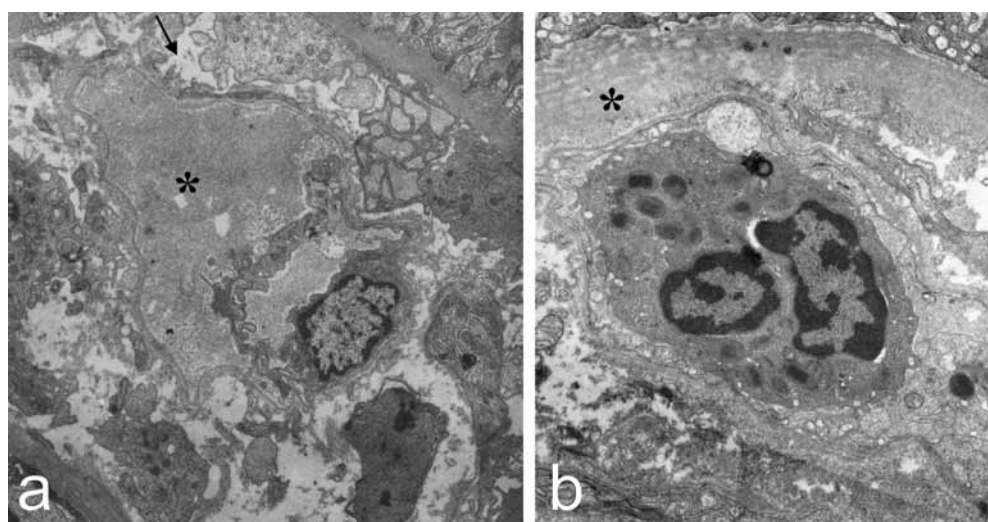


Figure 2. Kidney biopsy, electron microscopy: a (original magnification $\times 3,000$): marked interstitial edema (arrow) and peculiar lesions of peritubular capillary with a narrowed lumen due to interposition of a large space, filled with finely granular osmiophilic material (asterisk), between capillary basement membrane and endothelial cells. b (original magnification $\times 5,000$): polymorph eosinophils in peritubular capillary lumen. Thickening and multi-layering of the tubular basement membrane (asterisk).

dominal ultrasonographic examination and CT scan of the chest and abdomen were normal.

A left kidney biopsy was performed 2 days after admission. Light microscopic examination showed acute immuno-allergic interstitial nephritis with diffuse infiltration of the interstitium by inflammatory cells (neutrophils, lymphocytes, eosinophils and plasma cells), and tubulorrhexis (Figure 1). The glomeruli and vessels were unremarkable. Immunofluorescence study with antibodies specific for immunoglobulin light and heavy chains, C3, C1q and C4d complement components, was negative. By electron microscopy, severe

interstitial infiltrate was associated with interstitial edema parting the tubules. Severe lesions of peritubular capillaries characterized by separation of endothelial cells from peritubular capillary basement membranes (Figure 2), resulting in capillary loss were observed.

Tests for cryoglobulins, antineutrophil cytoplasmic antibodies, antinuclear and anti-DNA antibodies, anticardiolipin antibodies, anti-mitochondrial antibodies were negative. Levels of C3c, C3A, C4, CH50 and angiotensin convertase were normal. Blood and urine cultures, serologic tests for HIV, hepatitis B, hepatitis C, Hantavirus, leptospirosis, syphilis,

rickettsia and mycoplasma infections were negative.

Fluindione was stopped on the day of admission and calcium heparin was administered 4 days later, followed by oral acenocoumarol. Treatment with intravenous methylprednisolone pulses (250 mg/day, 3 days), followed by oral prednisolone (70 mg/day), resulted in a rapid improvement of the renal function. 15 days after admission, serum creatinine level was 1.1 mg/dl, microscopic hematuria had disappeared and eosinophils were within the normal range ($0.25 \times 10^9/l$). On the last follow-up, 5 months later, the patient's condition was excellent and clinical and laboratory data were unremarkable.

Discussion

AIN may occur as an adverse reaction to many different drugs, usually 2 weeks after exposure to the culprit drug but may occur sooner if the patient has been previously sensitized to the same agent [Perazella et al. 2005]. Clinical presentation of drug-induced AIN is variable and non-specific. Systemic signs of hypersensitivity, including fever, arthralgia and skin rash are present in as few as 15% of cases [Buysen et al. 1990]. These features are more common in penicillin-induced AIN, whereas they are frequently absent in cases related to NSAIDs [Markowitz et al. 2005]. Similarly, eosinophilia is observed in most penicillin-induced AIN cases, but in only 40% of other cases [Koselj et al. 1993]. As in our case, renal manifestations typically include acute renal failure, microscopic or macroscopic hematuria, sterile pyuria, eosinophiluria and low-grade proteinuria (< 2 g/d). Nephrotic range proteinuria may be present sometimes in patients with NSAIDs-induced AIN [Abraham et al. 1984].

Phenindione and fluindione are 2 drugs derived from indanedione. A frequency of 1.5–3% of hypersensitivity reaction has been reported with phenindione therapy [Naisbitt et al. 2005], including AIN in several cases [Kleinknecht et al. 1978, Kourilsky et al. 1982].

Fluindione was first implicated as a cause of AIN in 1991 [Gilson et al. 1991]. Since then, three cases of fluindione-induced AIN have been referenced in Medline [Grimaldi et al. 2005, Thurot et al. 2003] and 4 additional

cases have been recently reported in France [Coindre et al. 2005, Reynaud et al. 2005]. In most of these cases, the role of fluindione was not clearly proven. As fluindione was the sole medication in our patient, the present case strongly suggests that fluindione may be the responsible for severe acute renal failure secondary to diffuse AIN. Additionally, in our patient, the diagnosis of immunoallergic AIN was also suggested by systemic signs of hypersensitivity (fever with eosinophilia and eosinophiluria). Analysis of 6 of these cases showed that extrarenal signs are variable and inconstant in fluindione-induced AIN. Skin rash was found in two cases, fever in two cases, eosinophilia in two cases and arthralgias or hepatic cytolysis in one case. By contrast, acute renal failure and low proteinuria were invariably present. Microscopic hematuria was described in two patients and macroscopic hematuria in only one patient. These observations demonstrate that fluindione-induced AIN is a difficult diagnosis, which should be confirmed by kidney biopsy, as systemic symptoms may be absent and renal abnormalities are non-specific.

Little is known about the relationship between the risk of fluindione-induced AIN and duration and dosage of fluindione therapy. Renal prognosis does not seem to differ significantly in patients with AIN induced by fluindione, compared to those with AIN caused by other drugs. The condition usually resolves within several weeks after withdrawal of the offending agent [Markowitz et al. 2005]. Most patients diagnosed with fluindione-induced AIN had complete renal recovery, with only 1 patient requiring short-term dialysis [Reynaud et al. 2005]. Our patient was treated successfully with corticosteroids, but evidence for their use remains uncertain in drug-induced AIN [Clarkson et al. 2004] and withdrawal of the offending agent may be sufficient for renal recovery [Rossert et al. 2001].

On the basis of epidemiological studies, 1% of the French population is treated by vitamin K antagonists. Fluindione accounts for 77% of oral anticoagulant therapy in France [Libbey 1998]. Although fluindione-induced AIN is a rare complication, physicians need to be aware of this potential class reaction, as early recognition may prevent the development of severe renal injury.

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