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Teaching Point
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Fluindione-induced immuno-allergic interstitial nephritis

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Drug-induced acute interstitial nephritis (AIN) is an established cause of acute kidney injury (AKI). Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequent offending drugs [1]. Only a few vitamin K antagonist-induced AIN cases have been reported. Some publications describe AIN associated with fluindione (Previscan®), an anticoagulant of the antivitamin K family, derived from indanedione, exclusively marketed in France. We present an additional case of AIN secondary to fluindione and review the available literature.

A 70-year-old woman was hospitalized for AKI. Her treatment list included amlodipine and atenolol. In December 2007, the serum creatinine (SCr) level was 70 μmol/L and an asymptomatic atrial fibrillation was detected. Fluindione was hence initiated. SCr rose to 220 μmol/L (04/08). On admission, her SCr level had reached 3.4 mg/dL and fluindione was stopped. Blood pressure was 110/80 mmHg, and neither cutaneous rash nor peripheral lymphadenopathy was found. Laboratory tests showed SCr 299.2 μmol/L, proteinuria 2 g/24 h (1 g albumin and low-molecular-weight proteins, each) and negative urine sediment. A renal ultrasound revealed reduced-sized (10 cm) kidneys without obstructive uropathy. Immunological analyses were negative. A transjugular renal biopsy was performed. The renal biopsy included 11 glomeruli; 5 were sclerotic and 6 were normal. A diffuse infiltrate of lymphocytes, eosinophils and monocytes was found in the interstitium associated with severe tubulitis (Figure 1). Immunostains demonstrated CD3-positive lymphoid cells in the interstitium (Figure 2) compared to CD20 immunohistochemical staining (Figure 3). Immunofluorescence was negative. Electron microscopy was not performed. The diagnosis of fluindione-induced AIN (FI-AIN) was made. Despite withdrawal of the offending agent replaced by acenocoumarol, and oral corticosteroid therapy (1 mg/kg/day), renal function did not return to baseline values after 1 month (SCr, 259.6 μmol/L) but improved to 199.8 μmol/L 6 months later.

About 15% of the renal biopsies performed on patients with AKI demonstrate drug-induced AIN as the cause of the renal insufficiency. Only 13% of these patients showed the classic triad of rash, fever and eosinophilia. Discontinuation of the offending drug remains the first therapeutic step. Nevertheless, a considerable part of the affected patients may develop ESRD (23.4%). An important clinical prognostic factor is the average duration of the renal dysfunction; a cut-off point of 2–3 weeks seems relatively determining [1–3].

Few cases of vitamin K antagonist-induced AIN have been reported with warfarin, phenindione and fluindione [4]. Hypersensitivity reactions occur in 0.2–2% of cases [5]. Review of the literature revealed 16 biopsy-proven FI-AIN [5–11], including this case (Table 1). AKI appeared 7.5 ± 6.9 weeks (range 2–20) after introducing the offending drug. The average baseline SCr was (102.08 ± 35.2; range 62.5–149.6 μmol/L) obtained 7.5 ± 4.6 (range 0.5–16) months before the onset of FI-AIN. Fifty percent of patients showed proteinuria (0.3–19.7 g/24 h) associated with microscopic haematuria (12.5%) and leukocyturia (12.5%). The highest SCr reached between 135.52 and 824.56 μmol/L with a mean of 425.04 ± 243.76 μmol/L. Two patients (12.5%) required several sessions of haemodialysis [9]. Thirty-one percent (5/16) presented the classical triad of drug-induced AIN: fever, maculopapular rash and eosinophilia. The renal biopsy was obtained in 14 out of the 16 patients. In all cases, a diffuse inflammatory infiltrate composed of lymphocytes, eosinophils, monocytes and plasma cells invading the interstitial compartment was observed. Fluindione was withdrawn in all patients. Eleven patients (68.75%) were treated with steroids. Steroid doses and the duration of treatment were not uniform. The most common scheme consisted of oral prednisone (0.5–1 mg/kg/day) tapering off over 8–12 weeks. Intravenous pulses of methylprednisolone (250–500 mg daily

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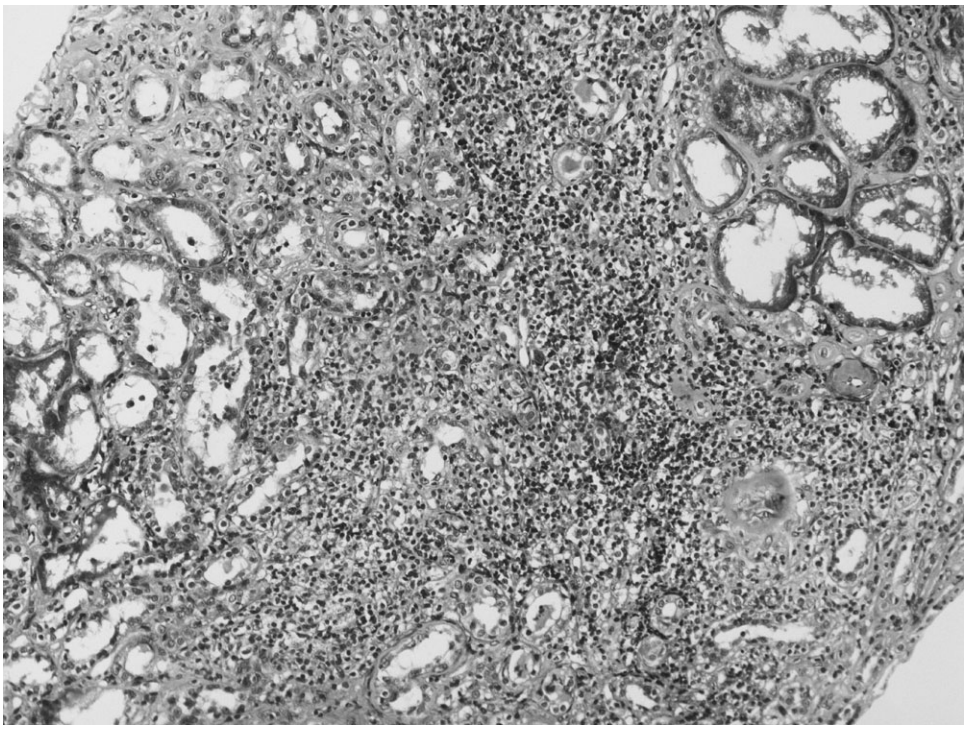

Fig. 1. Renal biopsy specimen showing expansion of the renal interstitium by large lymphocyte inflammatory cell aggregates and severe tubulitis. Masson's trichrome stain; original magnification ×40.

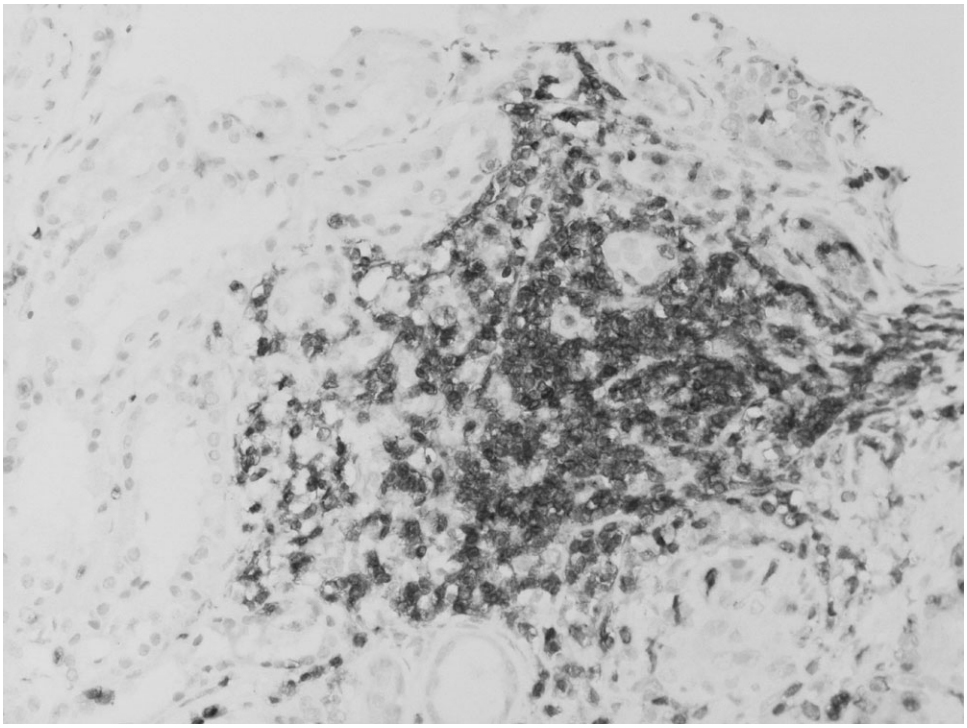

Fig. 2. Immunophenotyping analysis showing positive CD3 + T cells. Original magnification ×400.

Table 1. Characteristics of patients with fluindione-induced acute interstitial nephritis

Authors	Parameters									
	Sex	Age	Medical history	Fluindione indication	Interval between drug prescription and renal damage	Symptoms	Cutaneous patch tests	Kidney biopsy	Treatment	Outcome
Gilson *et al*. [6]	M	75	MI	Phlebitis	5 months	Non-oliguric ARF (from 62.5 to 135.52 μmol/L)	NA	Acute IN	Drug withdrawal, steroid	Renal function did not reach baseline values at 6 months
Sparsa *et al*. [5]	M	84	MI stroke	Atrial fibrillation	8 weeks	Non-oliguric ARF (from 88 to 374 μmol/L); fever, bronchial spasms, eosinophilia	Positive	Acute IN	Drug withdrawal, steroid	Complete recovery of baseline renal function after 5 weeks
	M	83	MI	Phlebitis	4 weeks	Non-oliguric ARF (147.84 μmol/L), proteinuria 0.43 g/day	Positive	NA	Drug withdrawal	Complete recovery of baseline renal function after 3 weeks
Thurot *et al*. [7]	M	68	Asthma	Atrial fibrillation	3 weeks	Non-oliguric ARF (88–136.4 μmol/L), haematuria, leukocyturia, proteinuria 19.7 g/day, fever, rash, eosinophilia	Positive	NA	Drug withdrawal	Positive reintroduction test; complete recovery of baseline renal function after 10 days
Coin *et al*.*	M	79	Heart failure	Atrial fibrillation	2 months	Non-oliguric ARF	Positive	Acute IN	NA	NA
Raynaud *et al*.*	3 M	46; 74; 70	CRF	Atrial fibrillation	3 weeks to 2 months	Non-oliguric ARF, fever, erythroderma, eosinophilia	NA	Acute IN	Drug withdrawal, steroid dialysis (one patient)	Positive reintroduction test; complete recovery of baseline renal function after 10 days
Grimaldi *et al*. [8]	M	73	CRF	Atrial fibrillation	5 weeks	Non-oliguric ARF (106.5–352.9 μmol/L), proteinuria	NA	Acute IN, tubulitis	Drug withdrawal	Complete recovery of baseline renal function after 2 weeks
	W	80	CRF	Phlebitis	4 months	Non-oliguric ARF (99.44–374 μmol/L), proteinuria 0.5 g/day	NA	Acute IN, tubulitis	Drug withdrawal	Death related to pulmonary embolism
Belmonaz *et al*. [9]	M	70	NA	Phlebitis	3 weeks	Proteinuria 0.3 g/day, fever, eosinophilia	NA	Acute IN	Drug withdrawal, steroid (IV pulses then oral)	Complete recovery of baseline renal function (SCr 1.1 mg/dL) after 2 weeks
Boulon *et al*. [10]	M	70	Diabete, HT, CRF	Phlebitis	3 weeks	proteinuria 0.3 g/day, fever, eosinophilia Non-oliguric ARF (149.6–759.44 μmol/L), proteinuria 3 g/24 h	NA	Acute IN, glomerular sclerosis	Drug withdrawal, steroid, dialysis	Renal function did not reach baseline values at 1 month (SCr 2.84 mg/dL)
Beauchamp *et al*. [11]	M	78	MI, diabetes	Atrial fibrillation	1 month	Non-oliguric ARF (735.7 μmol/L)	NA	Acute IN	Drug withdrawal, steroid	Positive reintroduction test; complete recovery of baseline renal function after 6 months
	M	72	BP cancer, diabetes	Atrial fibrillation	1 month	Non-oliguric ARF (86.24–824.56 μmol/day), proteinuria 0.4 g/day	NA	Acute IN	Drug withdrawal, steroid	Partial recovery of baseline renal function
	M	55	IgA nephropathy	AVR	15 days	Non-oliguric ARF (170.72–559.7 μmol/L)	NA	Acute IN, tubulitis	Drug withdrawal, steroid	Complete recovery of baseline renal function after 6 months
This case	W	70	Hypertension	Atrial fibrillation	5 months	Non-oliguric ARF (69.52–299.2 μmol/day), proteinuria 2 g/day	NA	Acute IN, tubulitis	Drug withdrawal, steroid	Ongoing

M, men; W, women; MI, myocardial infarction; ARF, acute renal failure; CRF, chronic renal failure; IN, interstitial nephritis; NA, not available; AVR, aortic valvular replacement; HT, hypertension.
*Not published.

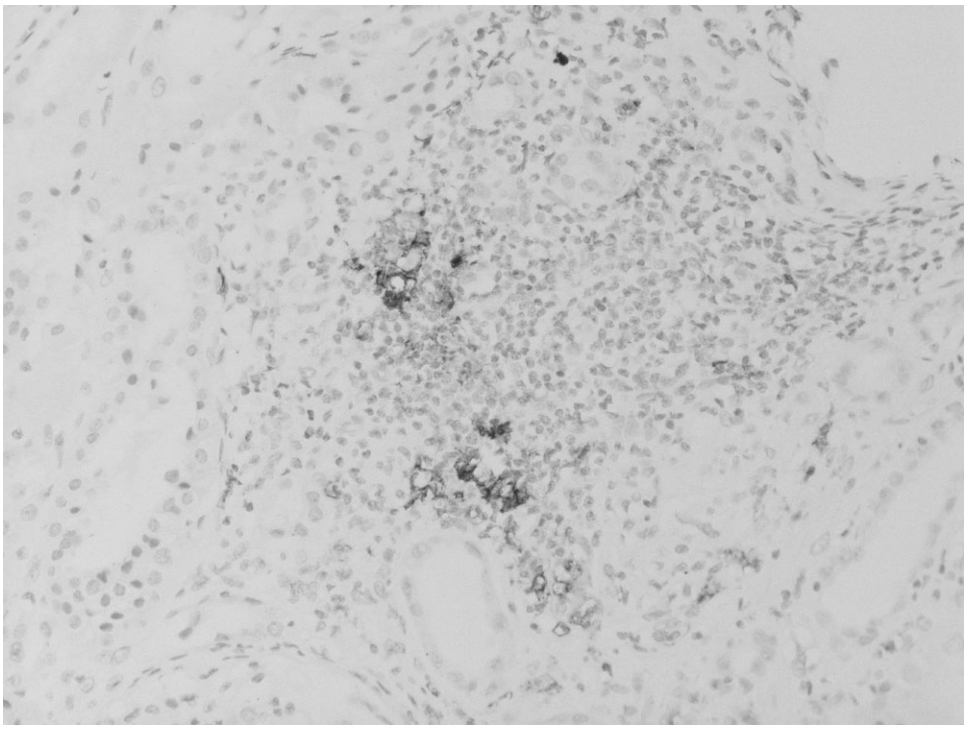

Fig. 3. Immunophenotyping analysis showing few CD20 + lymphocytes. Original magnification ×400.

for 3 days) were occasionally used. In 3 out of these 11 steroid-treated patients (27.3%), SCr never reached baseline values. The five patients who did not receive steroids had a complete recovery of baseline renal function 10 days to 3 weeks after withdrawal of the offending drug. However, the largest study to date by González *et al*. demonstrated the beneficial effects of steroids for the treatment of drug-induced AIN, especially when initiated soon after withdrawal of the offending agent [1].

Teaching point

Fluindione must be considered amongst drugs that induce AIN.

Conflict of interest statement. None declared.

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