

## A clinical case to solve...

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### ■ CLINICAL PRESENTATION

A 49-year-old Caucasian man was admitted in Intensive Care Unit for resistant hypertension, with need of labetalol intravenous perfusion.

His personal history was irrelevant, with previous normal arterial pressure. He travelled to Mozambique six week before and takes mefloquin for malaria prophylaxis.

Three week before admission, he presented low fever,odynophagia, rhinorrhoea and myalgia. He was not seen by a doctor and self-medicated with Ilvico N<sup>®</sup> (acetaminophen, brompheniramine and caffeine) for three days, without improvement. He had been then observed in an emergency room and medicated with levofloxacin for seven days, without amelioration. Ceftriaxone was prescribed after that. Two days after ceftriaxone beginning, he was admitted to hospital with severe hypertension.

On Intensive Care Unit admission, he presented normal temperature, resistant hypertension, oliguria, polypnoea, peripheral oedema, pleural and pericardium effusion.

Haemoglobin was 10.3 g/dl without leukocytosis or eosinophilia. C-reactive protein was 5 mg/dl and

serum creatinine was 6.8 mg/dl. Urinalyses showed haemoglobinuria without leucocyturia. Proteinuria quantification was 0.3 g/day.

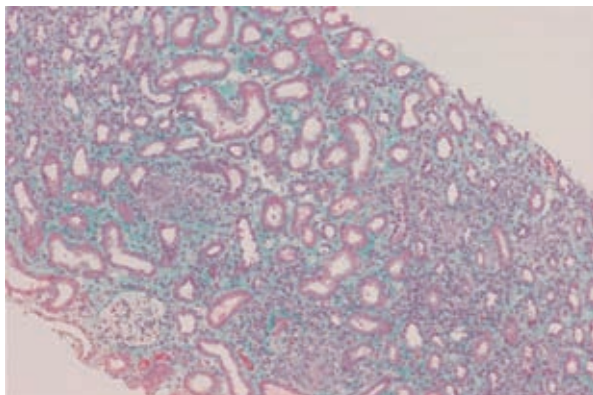
Renal echography revealed bilateral enlarged kidneys (right-140mm, left-141mm) with normal contours, increased parenchymal thickness and cortico-medular differentiation increment were related. Kidney lithiasis and urinary tract dilatation were excluded. The renal doppler was normal, excluding venous thrombosis.

In the third hospitalization day, a kidney percutaneous biopsy was done to clarify the acute renal failure.

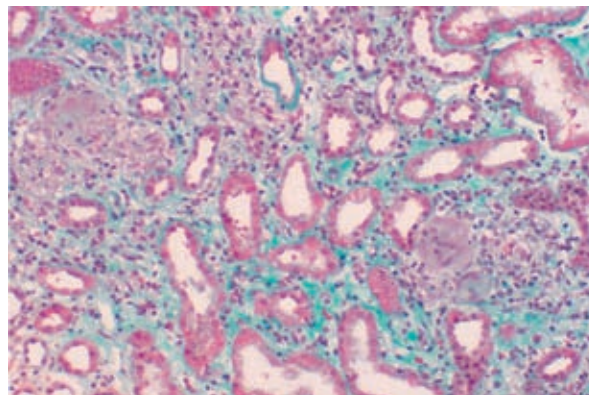
Only one histological specimen was collected and sent in formaldehyde to our laboratory. No frozen fragment was available for immunofluorescence. The fragment was paraffin-embedded for optical and immunofluorescence observation.

Immunofluorescence examination of the paraffin fragment was negative for interstitial or glomerular deposition of IgG, IgA, IgM, C3, C4, C1q, albumin and fibrinogen.

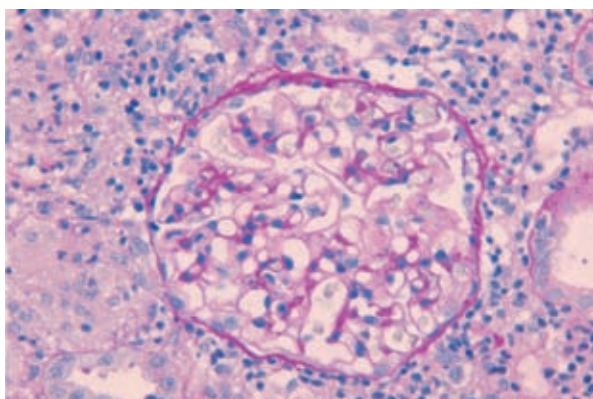
The main optical microscopy aspects are demonstrated in the following figures.



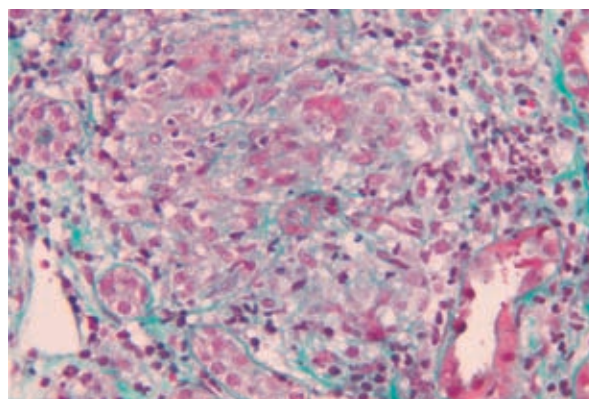
**Figure 1**  
Masson trichrome green (x100)



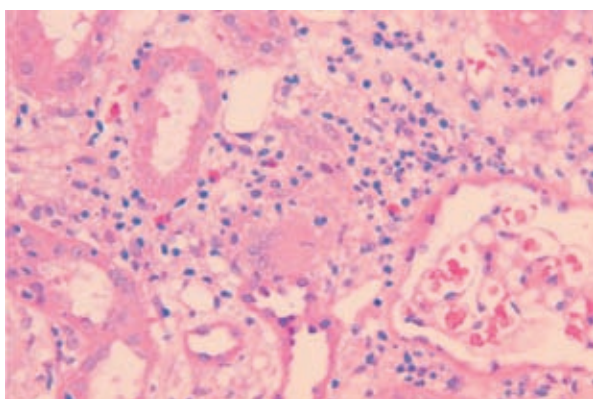
**Figure 4**  
Masson trichrome green (x200)



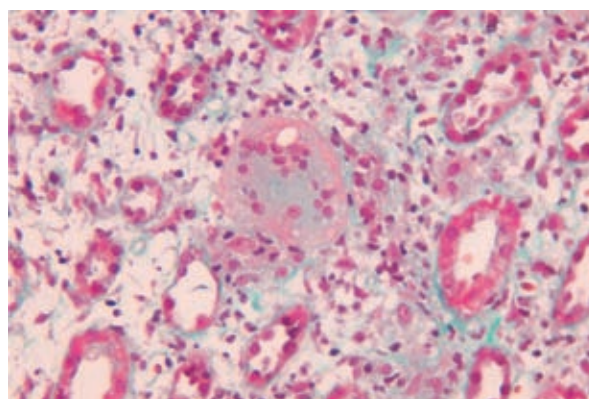
**Figure 2**  
Periodic acid-Schiff (x400)



**Figure 5**  
Masson trichrome green (x400)



**Figure 3**  
Haematoxylin-eosin (x400)



**Figure 6**  
Masson trichrome green (x400)

## ■ HISTOLOGICAL DIAGNOSIS

Figure 1 reveals extensive mononuclear inflammatory infiltrate, fibro-oedematous interstitium and focal acute tubular necrosis.

Figure 2 demonstrates a normal glomerulus and the presence of some lymphocytes in tubules- tubulitis. All the seventeen glomeruli and the blood vessels of this biopsy were normal.

In Fig. 3 we can observe the presence of interstitial inflammatory infiltrate of mononuclear cells and some eosinophils. A normal glomerulus is presented. An isolated multinucleated giant cell is visible.

In Fig. 4 we can see two non-caseous granulomas associated with multinucleated giant cells. This biopsy presents a total of nine granulomas.

Figure 5 shows a perivascular granuloma consisting of epithelioid histiocytes and lymphocytes.

Figure 6 presents an isolated multinucleated giant cell and interstitial fibro-oedema. These cells were scattered diffusely in the interstitium.

In summary, optical microscopy demonstrates normal glomeruli and blood vessels; acute inflammatory infiltrate, with predominance of lymphocytes and some eosinophils; fibro-oedematous interstitium, focal acute tubular necrosis; focal tubulitis; nine non-caseous granulomas with multinucleated giant cells.

Immunofluorescence examination and the Ziehl-Nielsen stain were negative.

The histological diagnosis was granulomatous acute interstitial nephritis.

## ■ COMPLEMENTARY EVALUATION

The urine was negative for BAAR direct examination and for bacterial culture.

The serum angiotensin-converting enzyme (ACE) concentration was normal. Antineutrophil cytoplasmic (ANCA) and anti-glomerular basement membrane (anti-GBM) antibodies were negative. Serology for HBV,

HCV and HIV were negative. Thoracic scan presented small bilateral pleural effusion and small pericardium effusion; absence of axillary, hilar, mediastinal adenomegalies and normal pulmonary parenchyma. Bronchoscopy was normal and no BAAR were identified in direct examination of broncho-alveolar specimen.

## Solving the case

## ■ DISCUSSION

Granulomatous interstitial nephritis (GIN) is a rare histological diagnosis, representing 0.5%-0.9% of total renal biopsies.<sup>1,2</sup>

The main causes of granulomatous interstitial nephritis, according to the review of 40 cases by Javaud *et al.*<sup>1</sup> are sarcoidosis (50%), drugs (17.5%), tuberculosis (7.55%), Wegener's granulomatosis (5%), leprosy (2.5%), *Mycobacterium avium* infection (2.5%), Crohn's disease (2.5%) and idiopathic (12.5%). In the review (n = 18) of Joss *et al.*<sup>2</sup>, TINU and drugs are responsible in the same percentage (11%) for GIN after idiopathic cases (50%) and sarcoidosis (28%).

Almost all drug classes have been implicated in acute interstitial nephritis: antibiotics (penicillins, cephalosporins, sulfonamides, vancomycin, rifampicin, tetracyclines, erythromycin and most others, if not all); NSAIDs; diuretics (thiazides, furosemide, triamterene); antiviral (acyclovir, foscarnet, indinavir); and miscellaneous drugs (phenytoin, allopurinol, cimetidine, captopril, lithium, valproate, warfarin, interferon, lamotrigine).

The presence of granulomas is most often reported after the use of ampicillin, methicillin, penicillin, rifampicin, furosemide, allopurinol and phenytoin<sup>3</sup>.

From the literature review, we found a case of levofloxacin inducing GIN<sup>4</sup>.

The mainstay of therapy for drug-induced AIN is timely discontinuation of the causative agent.

## ■ Anatomico-clinical diagnosis

Drug-induced acute interstitial nephritis.

## ■ Treatment and evolution

The patient's creatinine started downloading on the fourth day. After histological diagnosis, fifth day after admission, three consecutive 1 g daily pulse of methylprednisolone were administered, with rapid improvement of the kidney function. No oral corticoids were prescribed. Currently, tree months after acute renal failure, the patient's serum creatinine is 1.2 mg/dl, with a normal urinalysis.

## References

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2. Joss N, Morris S, Young B, Geddes C. Granulomatous interstitial nephritis. *Clin J Am Soc Nephrol* 2007;2(2):222-230
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4. Ramalakshmi S, Bastacky S, Johnson JP. Levofloxacin-induced granulomatous interstitial nephritis. *Am J Kidney Dis* 2003 Feb;41(2)

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