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Caso clinico

Case report

Irreversible acute renal failure and cholestatic hepatitis following therapy with indomethacin in an HIV-naïve patient with pericarditis: a case report

Insufficienza renale acuta irreversibile ed epatite colestatica in corso di terapia con indometacina in un paziente HIV-naïve con pericardite

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INTRODUCTION

Echocardiographic studies have identified a pericardial effusion in approximately 20 per cent (range 10 to 40 per cent) of patients with AIDS [1-3]. In many cases pericarditis has a brief and self-limiting course. On the other hand, treatment of pericarditis remains largely empirical owing to a relative lack of randomized controlled trials and NSAIDs (nonsteroidal inflammatory drugs) are the most credited option [4]. Indomethacin is a widely used NSAID and inhibits the activity of cycloxygenase by decreasing the formation of the precursors of prostaglandins and thromboxanes from arachidonic acid or by activating peroxisome-proliferator activated receptors.
Indomethacin is generally considered safe and well tolerated but it can provoke acute interstitial nephritis and acute renal failure due to a decreased prostaglandin synthesis and renal ischemia. In healthy adult patients the incidence of renal adverse effects is less than 1% and the risk increases with age because of concomitant renal disease, diabetes, diuretics and congestive heart failure [5]. Indomethacin-induced renal failure is usually reversible after the drug is stopped [6-10]. Rare cases of indomethacin-induced hepatitis, cholestasis and jaundice have been reported and several studies carried out on animals show the hepatic toxicity of indomethacin [11, 12]. We describe a case of acute renal failure and cholestatic hepatitis following therapy with indomethacin in a patient with AIDS and pericarditis starting HAART (highly active antiretroviral therapy).

CASE REPORT

A 54-year-old man was admitted to our Infectious Diseases Department of the University Hospital of Palermo in September 2012 because of fever and chest pain. He was an MSM and had experienced a 40 kg weight loss during the previous year. His clinical history was unremarkable, except for a bipolar disorder. On physical examination he had oral candidiasis and paraphonic tones all over the precordium. On neurological examination he presented bradylalia and psychomotor slowing.
On admission ELISA anti-HIV serology and Western Blot test were performed and HIV in-

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fection was diagnosed. An electrocardiographic exam showed sinus tachycardia (PR 100 bpm), isolated ventricular ectopic beats, PR interval upper reference limits and abnormal repolarization. Pericardial effusion was evident on echocardiographic exam and pericarditis without haemodynamic impairment was diagnosed. Indomethacin (50 mg TID) was administered. Upon admission the CD4 T-cell count was 2/mmc (1.41%) and HIV-RNA 588,000 copies/ml. Antiretroviral treatment with darunavir/ritonavir 800/100 mg once a day and tenofovir/emtricitabine and prophylaxis for OIs with cotrimoxazole and azitromycin was started. Serology for syphilis, toxoplasmosis, B and C hepatitis resulted negative and renal and liver function were within normal values (GOT/GPT 13/11 U/L; total and direct bilirubin respectively 0.35 and 0.22 mg/dl, creatinine 0.91 mg/dl, BUN 34 mg/dl, GFR 120 ml/min/1.73 m^2). White cells blood count was 1700/mmc, haemoglobin was 8.2 g/dl and platelets were 110,000/mm^3.

A few days after admission fever and chest pain disappeared and we observed a mild reduction of pericardial effusion on echocardiography and electrocardiographic normalization but the patient developed watery diarrhoea without mucus or blood. The direct faecal exam revealed the presence of *Cryptosporidium* spp. Clinical conditions and laboratory tests progressively worsened and liver and renal dysfunction appeared (total and direct bilirubin 12.4/11.13 mg/dL, creatinine 2.37 mg/dL, BUN 104 mg/dL, GFR 30 mL/min/1.73 m^2). HAART with tenofovir/emtricitabine was replaced with lamivudine and raltegravir and boosted darunavir was continued but renal and liver function rapidly plummeted (total and direct bilirubin 16.65/14.31 mg/dL, creatinine 5.42 mg/dL, BUN 232 mg/dL, alkaline phosphatase 516 mg/dL). Indomethacin was suspended and the patient had to receive dialysis. During the remaining hospitalization a liver function improvement (total and direct bilirubin 3.59/2.96 mg/dL) was observed but renal dysfunction was irreversible despite dialysis.

DISCUSSION

Severe renal impairment becomes a major concern in patients with HIV infection above all if they are assuming antiretroviral treatment containing tenofovir. Tenofovir has been associated with chronic renal dysfunction and Fanconi syndrome, especially in the setting of multifactorial causes for renal damage or in patients with underlying renal disease [13]. In the literature, to date, four cases of acute renal failure in patients assuming tenofovir and NSAIDs have been described but all of them presented other important factors of renal dysfunction [14]. Several NSAIDs have been associated with liver damage as well [15]. Our patient did not have other risk factors for renal damage apart from HIV infection and an antiretroviral treatment including tenofovir administration seemed the most appropriate choice. In spite of this he experienced at the same time acute renal failure and cholestatic hepatitis probably due to a drug-drug interaction between antiretroviral drugs, antibiotics used for OI prophylaxis and indomethacin. Dehydration occurring during *Cryptosporidium* spp enteritis probably contributed to reduced renal perfusion and to lasting damage. Based on this case we think more attention should be paid when several drugs are used in this kind of patient and a dose adjustment could be necessary to avoid rapid life-threatening renal deterioration.

Keywords: indomethacin, tenofovir, acute renal failure, pericarditis, cholestatic hepatitis.

SUMMARY

The most frequent clinical manifestation of cardiovascular diseases in patients with AIDS is pericarditis. Indomethacin is a well tolerated non-steroidal inflammatory drug (NSAID) widely used in the treatment of pericarditis but it can provoke acute renal failure. Tenofovir has also been associated with chronic renal dysfunction. Liver damage can occur during treatment with NSAIDs. We describe the first case of acute renal failure and cholestatic hepatitis occurring in an HIV-naïve patient with pericarditis starting HAART (highly active antiretroviral therapy) and assuming indomethacin and antibiotic therapy for opportunistic infections (OIs) at the same time. Based on our case we suggest that attention be paid to drug-drug interactions in such patients.

RIASSUNTO

La pericardite è la più frequente manifestazione clinica a carico dell'apparato cardiovascolare nei pazienti con AIDS. L'indometacina è un farmaco antinfiammatorio non steroideo (FANS) ben tollerato e ampiamente usato nella terapia della pericardite ma può causare insufficienza renale acuta (IRA). Anche il tenofovir è stato associato alla comparsa di danno renale. L'aumento degli indici di funzionalità epatica è stato descritto in corso di terapia con FANS. Il nostro è il primo caso clinico riportato di IRA ed epatite colestatica in un paziente HIV-naïve con pericardite che iniziava la terapia antiretrovirale e assumeva allo stesso tempo indometacina e terapia antibiotica per la profilassi delle infezioni opportunistiche. Sulla base della nostra esperienza, molta cautela deve essere posta nella gestione delle interazioni farmacologiche in questo tipo di pazienti.

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