Acute interstitial nephritis associated to omeprazole therapy

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Abstract

Acute renal failure is a common problem found in our internal medicine wards. In terms of differential diagnosis, acute interstitial nephritis (AIN) is one of the easily forgotten possibilities mainly when several comorbidities (namely neoplastic or infectious) are present and patients take several medicines, making difficult (if not impossible) to identify the causing drug. The authors report a case of AIN, confirmed by renal biopsy, in a patient with peptic ulcer taking omeprazole for 2 years.

Key words: acute interstitial nephritis, acute renal failure, omeprazole.

Introduction

Acute interstitial nephritis (AIN) is a main cause of acute renal failure featured primarily by an inflammatory infiltrate at interstitial level.[1,2] Since its first description, by Coucilman, in 1898, of an AIN case associated to diphtheria and scarlet fever,[1] many have been the causes implied as etiology factors, being hypersensitivity to drugs reactions among the most prevalent, emerging from the growing use of all drugs groups.[1,2,3] In spite of many drugs being implicated, their frequency changes a lot, being antibiotics and anti-inflammatory drugs among the most prevalent.[2,3]

Omeprazole is a proton pump inhibitor widely prescribed to peptic ulcer disease and gastroesophageal reflux conditions, although usually it is well tolerated.[4,5] The first AIN case induced by omeprazole was described in 1992 by Ruffenach *et al* [6] and several cases have been reported ever since. In 2004 were reported the first cases related with other proton pump inhibitors (PPI).

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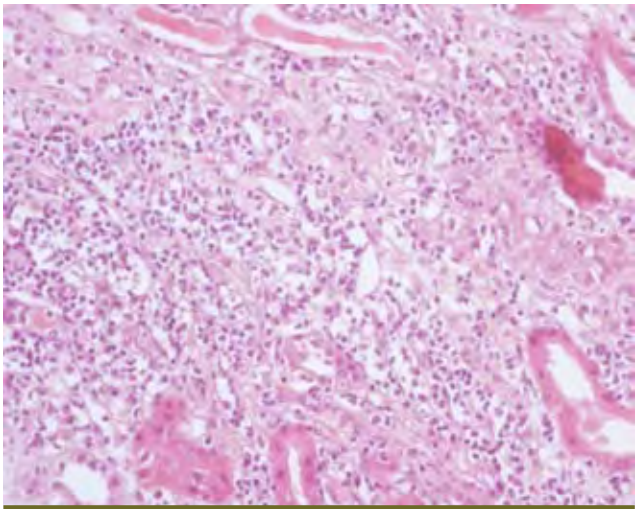
Clinical case

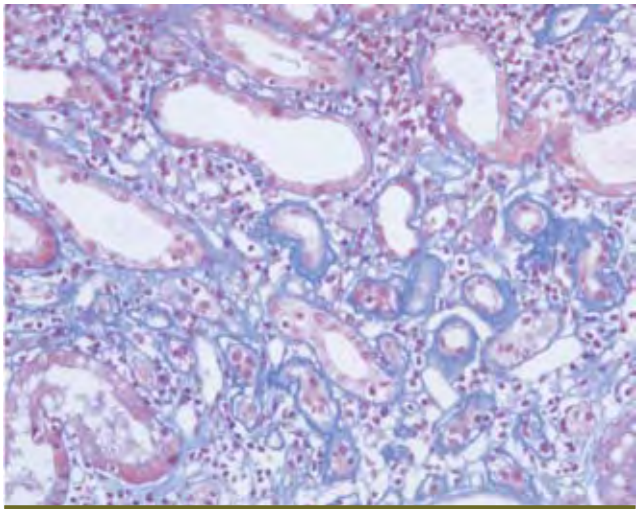
An 80 years-old male patient, with hypertension history, chronic kidney failure (basal creatinine 1.6 mg/dL with an estimated clearance of 40), hyperuricemia, dyslipidemia, chronic venous insufficiency and gastric ulcer known since 2003. Without any other history (namely family history). His regular medication has been lisinopril, clopidogrel, pentoxyphiline, alprazolam and omeprazole over the last 2 years (irregularly). There were no references to allergies or other reactions to drugs.

In March 2005 this patient was admitted for the first time in our hospital, with epigastric pain associated to anorexia, nausea, vomiting for the last couple of months. He denied fever, arthralgia, rash, breathing or urinary complaints. The objective exam showed no alterations, except for the *livedo reticularis* (mainly at lower limbs level). On admission, he had the following values hemoglobin 10.9 g/dL, leukocytes 7000/mm^3 with 62.5% neutrophils (4400/µL) and 3.1% eosinophils (200/ µL), platelet count 168000/mm^3, urea 131 mg/dL and creatinine 3.8 mg/dL. The patient was admitted and initially treated with endovenous fluid therapy, lisinopril 20 mg/day, omeprazole 20 mg/day and alprazolam 0.5 mg/night. From the assessment made it should be highlight: type II urinalysis with proteinuria (160 mg/dL) and 100 leukocytes/µL without growth in culture tests; kidney ultrasound showing normal size kidneys with increased cortical echogenicity without obstruction; negative serology for A, B and C hepatitis, Human immunodeficiency virus, cytomegalovirus or Epstein-Barr, syphilis, toxoplasmosis, Legionella or Mycoplasma. Auto-immune systemic diseases markers (namely rheumatoid factor,



Renal biopsy showing a lymphocytic interstitial infiltrate with plenty of eosinophils, histiocytes and plasmocytes (H & E 40x).

FIG. 1



Tubules show a cystic dilation. It should be noticed the integrity of the glomerular membrane (trichrome staining 100x).

FIG. 2

anti-nuclear antibodies, neutrophil anticytoplasm antibody and complement) were all negative. During admission, his kidney function got worst progressively with a maximum creatinine of 4.9 mg/dL.

After suspending all medication, he underwent kidney biopsy on the 13th day, showing "nephroangiosclerosis and acute interstitial nephritis lesions with mixed inflammatory cell infiltrate at interstitial level" *(Fig. 1 e 2)*. In this period of time, and without taking any medication, the patient´s kidney function has significantly improved (from a 4.9 mg/dL creatinine to a minimum value of 2.1 mg/dL).

After the kidney biopsy, lisinopril and omeprazole were simultaneously readministered with new analytical deterioration (reaching a maximum creatinine of 4.8 mg/dL). Alternating the suspension of drugs, it was after omeprazole withdrawal that serum creatinine returned to 1.7 mg/dL (to values close to 2 years ago: 1.6 mg/dL).

Discussion

Acute interstitial nephritis accounts for 5% of patients undergoing investigation due to unexplained kidney failure.[3,5] Although there are several AIN causes (namely auto-immune, neoplastic or infectious), at present the cases related with drugs are the most prevalent[1,2,3] *(Table I)*. From all drug groups acknowledged to causing AIN, proton pump inhibitors account for 7% of the total.[7] The clinical condition shows typically unspecific symptoms including general malaise, anorexia, nausea and vomiting. The clinical spectrum ranges from asymptomatic increases in the renal function or changes in the urinary sediment up to hypersensitivity conditions with fever, rash and eosinophilia;[1,2,3] once such classic triad is present only in 5% of the cases, a high degree of suspicion is always necessary. The only positive datum in the objective exam was the presence of *livedo reticularis* important to frame, in this context, as it could be an atheroembolism (not confirmed), as no other sign or symptom was present, namely autoimmune, which could point out to an alternative diagnosis.

To acknowledge such entity is of extreme importance, as the condition will always re-occur once the drug is reintroduced (as happened with our patient).[5,6] It should also be highlighted that these cases induced by drugs are not dose-dependent; its precise cause is unknown (although the key mechanism seems to be induced by an antigen), what makes AIN an unpredictable event.

As there is no other analytical diagnostic approach, renal biopsy remains the gold-standard to establish unequivocally the diagnosis.[1-7] However, it is not compulsory to have it done in all patients, in cases where the possible triggering drug can be easily withdrawn or in patients who improve after the withdrawal of all possible causing agents.[1]

AIN treatment is mainly based in support thera-

TABLE I

1. Infections Bacterial *Corynebacterium diphteriae, Legionella, Staphylococci, Streptococci, Yersinia* Viral Cytomegalovírus, Epstein-Barr virus, hantavirus, hepatitis C, herpes simplex, human immunodeficiency virus Other *Leptospira, Mycobacterium, Mycoplasma, Rickettsia, Tseponema pallidum, toxoplasma gondii*
2. Auto-imuune Transplant acute rejection, systemic erythematous lupus, Necrotizing vasculitis, glomerulonephritis
3. Neoplam Discrasias plasmocitárias, doenças linfoproliferativas
4. Drugs* Antimicrobial (ampicillin, ciprofloxacin, meticillin, G penicillin G, rifampicin, sulphonamide), non steroidal anti-inflammatory (acetylsalicylic acid, fenoprofen and ibuprofen, indomethacin, piroxicam), pain killers, anticonvulsivants (phenytoin), diuretics (furosemide), others (allopurinol, cimetidine and omeprazole)
* the most frequent drugs involved are highlighted

py. After a presumption diagnosis (or histologically confirmed, as in our patient) all drugs potentially causing AIN must be suspended (assuming that all other possible etiologies were considered and excluded).[2,3] After omeprazole withdrawal, a progressive recovery of the renal function was observed in the two following weeks for values deemed as baseline. If an early withdrawal is made, we can expect in most patients, a recovery to a renal function within normal/almost normal values. If this is not made, it must be taken into account the possibility these patients will progress towards a chronic kidney disease.[2]

In terms of therapy, a considerable controversy still remains regarding the role of immunosuppressants namely glucocorticoids. There are no prospective random studies supporting the use of glucocorticoids in AIN treatment, namely to speed up the renal function recovery time or baseline values improvement.[3,5,6,8,9] If one decides that corticotherapy is a reasonable approach, it can be administered prednisone 1 mg/Kg/day, orally for 2-3 weeks, with a gradual weaning off in the 3th-4th following weeks. In patients not responding for 2-3 weeks it should be considered treatment with cyclophosphamide.[1-7]

Proton pump inhibitors drugs are a class of antiulcer drugs widely used (and in a growing way). They show a good oral bioavailability, a wide link to plasma proteins, a metabolism by hepatic cytochrome P450 CYP2C19, with renal excretion of inactive metabolites. In spite of not being nephrotoxic drugs in innate form, there has been several cases of AIN linked to omeprazole (at least 29 cases between 1992 and 2004) and from 2004 onwards a growing number of cases related with other proton pump inhibitors, coming to the conclusion that probably is a class effect,[10,11] in spite of being, as we saw, idiosyncratic reactions.

Conclusion

In spite of AIN cases resulting from AIN therapy with proton pump inhibitors being uncommon, they should always be included in the differential diagnosis of unexplained acute kidney failure, as it is a pathology with potential to progress to chronic kidney disease, being a highly treatable disease. This is still more important if we take into account the universe of patients treated by resident physicians, responding to several comorbidities and to multiple medications liable to cause such condition. The authors emphasize the difficulty to identify the responsible drug (after excluding all other causes), even if this deals with a small number of involved substances (as it was our patient case). ■

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