Dear Editor,

Granulomatous hepatitis is characterized by the appearance of fever and the finding of epithelioid granulomas in the liver of unknown aetiology. It can show itself as the first manifestation of a systemic disease.

The clinical findings are scarce and related mostly to the basic pathology, fever being the most common of the initial symptoms, followed by constitutional syndrome, hepatomegaly and sometimes portal hypertension. Laboratory findings in the first stages include slight increases in hepatic enzymes and alkaline phosphatase.

The aetiology for this picture encompasses different causes, form infection: bacterial (TB, Coxiella, Brucella), viral (CMV, EBV), adverse drug reactions (allopurinol, carbamazepine, halothane), to systemic pathology (Chron’s disease, sarcoidosis); the most frequent being TB, primary biliar cirrhosis and adverse drug reactions (1).

We are presenting a case-study of one patient with granulomatous hepatitis secondary to treatment with allopurinol, aggravated by posterior addition of furosemide as treatment for hypercalcaemia.

A perusal of literature in PubMed (key words: allopurinol, granulomatous hepatitis), with no limits for date of publication or written language enabled us to find a meagre account for some ten published cases and only on case we found a coincidence for a clinical worsening when furosemide was concomitantly used with allopurinol in the course of the granulomatous hepatitis process.

Case clinical

Our patient is a sixty two years old man who was admitted to hospital with a history of type II diabetes mellitus, hyperuricemia, and presenting a constitutional syndrome. His main symptoms were loss of weigh, poor appetite and hypercalcaemia.

Routine blood tests showed hemoglobin 9.9 mg/dl, eosinophils 7.5 percent in WBC, TGG 225 U/L, calcium 11.8 mg/dl, total proteins 7.2 g/dl. Creatinine 1.5 mg/dL, ACE 134.8, antinuclear antibodies negative results. Serology for hepatitis, CMV, EBV, toxoplasma, Aspergillus fumigatus, Brucella and candida were negative.

Upper gastrointestinal study, colonoscopy, bronchoscopy, gammagrapy, proteinogram and bone marrow biopsy were normal.

Abdominal ecographic study and thoraces-abdominal TC showed a diffuse hepatitis associated to portal hypertension.

After receiving furosemide and serum therapy to lower the level of calcium, this instead increases to 14.7 mg/dl. A liver biopsy then showed evidence of epithelioid granulomas with fibrotic changes, without necrosis. Microscopic findings were of giant polinucleated epithelial cell (some with microvacuoles) as well as plasmatic, mononuclear and polymorphonuclear cells; the affected tissue surpassing the portal boundary with macrovesicular estesatosis, neutrophils and eosinphils. Tintion for fungus and Ziehl was negative.

As the clinical picture pointed to a pharmacological adverse reaction to both allopurinol and furosemide, they then were removed. Three weeks thereafter the level of calcium was still high (10.7 mg/dl), a reason for us to initiate a short cycle of corticosteroid therapy with the result of a total recovery to normalcy for calcium level and hepatic enzymes after some two months. Ecographic abdominal study rendered an equal return to normal at the fourth month.
Discussion

Allopurinol is being used for the treatment of hyperuricemia and gout for a long while. The common side effects are related to the skin. Gastrointestinal and genito-urinary systems, with hepatotoxicity as a rare occurrence, manifesting itself mostly as a reversible hepatitis, granulomatous hepatitis, acute liver failure and vanishing bile duct syndrome (2-5).

Granulomatous hepatitis as secondary to treatment with allopurinol is a rare entity, as shown by the scant literature available, in spite of the fact that it is a known side effect of the drug, regardless of its rarity (6-8). The anatomopathological findings in the registered cases vary from one to another study. Suspicion arises then with the appearance of a compatible histopathology, a temporal relationship an improvement of the clinical picture when the product is taken off.

In our case-study the increased levels for calcium and the hepatic enzymes were further elevated as soon al furosemide was added to treatment (in an effort to lower hypercalcemia).

In one of the published cases a similar conclusion was reached, blaming the combined use of those drugs as the cause for the severe side effects of interstitial nephritis and granulomatous hepatitis (8).

As for differential diagnosis and after ruling our infection (mostly TB) we focused on hepatic sarcoidosis (6,9), an entity by itself diagnosed from other pathologies by mere exclusion.

As our patient derived a frank recovery after withdrawal of the above drugs together with the prescribed use of a short cycle of corticosteroid therapy leading to a complete resolution of the clinical picture, the diagnosis was the firmly established as an adverse drug reaction granulomatous hepatitis, due to allopurinol and further aggravated with the addition to therapy for furosemide.

We recommend to keep in mind the above finding whenever hepatic lesion arise in the course of treatment with allopurinol and to avoid the concomitant prescription of furosemide in such event. We look forward to hear of other studies related to the above.

References

7. Stricker BH, Blok AP, Babany G, Benhamou JP. Fibrin ring granulomas and allopurinol Gastroenterology 1989; 96; 1199-203.