Hyperacute fulminant fungal peritonitis and ascites in a HIV-infected patient with HCV-related, compensated liver cirrhosis. A supportive role for prolonged nimesulide self-administration?

A rare case of *Candida albicans* fulminant fungal peritonitis in a patient co-infected with HIV and HCV, no prior history of decompensated liver cirrhosis, and no histopathologic signs of liver and/or kidney acute toxicity, possibly associated with exaggerated self-administered nimesulide consumption and a potential pathogenetic pathway raised by some experimental studies, is reported and discussed.

An i.v. drug addict had HIV infection discovered 14 years before, and was treated with lamivudine-stavudine since 6 years with a stable course: HIV-RNA copies 480/ml, CD4+ count 428 cells/μl. After detection of a chronic HCV infection in 1998, neither invasive diagnostics nor specific treatment was performed, due to an apparently mild-stable liver disease with a slight-intermittent ALT-AST elevation, and absence of cholestasis signs. Repeated abdominal ultrasonography showed a moderate hepato-splenomegaly with hyperintense liver structu-

re. Our patient denied further examination (including liver biopsy), since he repeatedly deferred any attempt of antiviral therapy for chronic HCV infection. Two months before admission, our patient suffered from a right shoulder fracture. Thereafter, nimesulide (100 mg, 2-3 times per day) was self-administered by our patient during at least 6 consecutive weeks, because of pain and functional impotence. An unexpected and rapidly worsening abdominal pain and distention, mounting fatigue and tachypnea, and oliguria (never suffered before), led to immediate hospitalization. Laboratory exams upon admission showed a slight increase of serum ALT (65 U/l), amylase (79 U/l), and bilirubin (3.2 mg/dl) levels, with a mild decreased albumin (2.8 g/dl), while no significant abnormalities were detected, save an altered blood coagulation (prothrombin value 43%, aPTT ratio 1.5, INR value 1.7) A globose but treatable abdomen with abundant ascites, and rapidly increasing peripheral edema were the prominent signs. A potent diuretic therapy (i.v. furosemide, 20 mg 5 times daily, and potassium canrenoate at 200 mg/day), and albumin administration (100 ml daily), were carried out during the first admission day, failing in reverting the disease course, which resulted in an increased ascites effusion and anuria. An immediate paracentesis allowed the recovery of 3,500 ml of corpuscular ascitic fluid (containing > 1,000 neutrophils/μl), compensated by albumin administration. The introduction of amilopidine, chlorthalidone, slow furosemide administration (20 mg thrice daily), and spironolactone (50 mg/day), together with meropenem coverage, were carried out. Anuria never ameliorated, and was accompanied by overwhelming laboratory signs of kidney insufficiency and need for fluid-electrolyte adjustement, while arterial gasanalysis did not show anomalies, and fever was never observed. Within 24 hours of admission, our patient deceased with untreatable pulmonary edema, and necropsy examination showed a diffuse polyvisceritis, a chronic micronodular liver cirrhosis with abundant yellowish ascites formation, while the final cause of death proved to be pulmonary edema. The histopathological study of the liver showed an overall Knodell score of 9, depending on cirrhosis (5), portal inflammation (2), and bridging necrosis (2). No significant macroscopic abnormalities were detected as to kidney and urinary tract. Diffuse pericardial-pleural adherences were found, and all abdominal organs were involved by a superficial inflammatory process, and ascites deposition. Subsequent histopathologic examinations of different organs did not add significantly, and signs of liver and/or kidney acute toxicity were carefully excluded at histopathological exam. On the day after patient's death all cultures of ascitic fluid yelded an isolated *C. albicans* strain (susceptible to all tested antifungal agents), in absence of other positive microbiological assays.

Non-steroidal anti-inflammatory drugs (NSAID) have been implicated in multiple anecdotal episodes of severe and infrequently lethal hepatic toxicity[1-3]. In particular, nimesulide has been associated with serious or life-threatening hepatic and/or kidney failure[1,4]. A recent coho rt study estimated the risk of acute liver toxicity associated with nimesulide compared with other NSAID, by examining almost two million NSAID prescriptions carried out in the Umbria region of Italy in a 5-year period[2]. NSAID use proved associated with a 1.4 increased risk of hepatopathy during time, while in current nimesulide users the rate for all hepatopathies and overall liver injury proved 1.3 and 1.9, respectively[2]. However, in our case the prolonged (6-week) nimesulide self-administration did not cause direct, acute liver and/or kidney toxicity (as assessed by histopathology), although an underlying HCV-related, compensated liver cirrhosis was already present, as established at necropsy, while the rapid deterioration of laboratory parameters led to a Child-Pugh score of B-8, upon admission. The exceedingly rapid and severe evolution towards a *Candida albicans*-infected ascites formation, associated with refractory anuria and final death determined by pulmonary edema, are remarkable. This last clinical course (rapid ascites formation in absence of a previous, decompensated liver cirrhosis, acute hepatotoxicity and kidney involvement at autopsy studies), was never observed after NSAID/nimesulide administration, so that alternative pathogenetic mechanisms may be hypothesized. Added to the prostaglandin inhibition involving renal artheriolar system, an animal model demostrated an early, increased intestinal vascular permeability mediated by vasoactive mediators released by resident peritoneal macrophages and mast cells, and causing infectious peritonitis in mice, after the administration of NSAID-like agents[5]. An impaired phagocytic activity of neutrophils of healthy subjects has been also demonstrated by *ex-vivo* models, after nimesulide adjunct to the culture medium[6]. Furthermore, while a polymicrobial infection is usually expected when intrabdominal infection or infected ascites are of concern[7], isolated *Candida* infection infrequently occurs, also in absence of prior, prolonged broad spectrum antibiotic administration (like in our case). Isolated intrabdominal *Candida* infection, although remaining a rare but probably understimated event, is usually related to peritoneal dyalisis, infection of central intravascular catheters, or local abscess formation[8]. Although less frequent compared with bacteria, the isolation of *Candida* spp. from cirrhotic ascites may occur, and its clinical role is still debated, according to a recent retrospective survey[9]: in this series, symptomatic cases and those related with peritonitis and/or an ascitic fluid neutrophil count > 315 cells/μl were linked with a severe, often lethal outcome. In our case, an isolated *C. albicans* infection could not be suspected in our HIV-infected patient, since he lacked of evident immunodeficiency and prior antibiotic administration, and could not receive an adequate therapy, since the yeast growth occurred after death. Physicians who face patients with non-decompensated liver cirrhosis should remind that all NSAID derivatives may act also indirectly on liver, bowel, and kidney function, and could prompt an end-organ damage, possibly complicated with infectious ascites, which is not necessarily bacterial in origin, but may be polymicrobial or also of fungal origin[9,10], especially when an underlying, advanced HIV disease is present. The pathogenetic basis of ascites decompensation of chronic hepatitis and infectious peritonitis should deserve further investigation, as well as the consideration of possible indirect toxicity of NSAID agents on both gut and local immune system cells.

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