Granulomatous hepatitis and hemophagocytic syndrome after bacillus Calmette-Guerin bladder instillation

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SUMMARY

Intravesical instillations of bacillus Calmette-Guérin are frequently used for treating superficial bladder carcinoma which is considered a safe treatment. We describe an unusual complication with hemophagocytosis and granulomatous hepatitis. Prompt diagnosis and treatment with corticosteroids, anti-tuberculous agents and intravenous immunoglobulins led to a rapid recovery.

RÉSUMÉ

Les instillations intra-vésicales de bacilles de Calmette et Guérin sont fréquemment utilisées pour le traitement du carcinome superficiel de la vessie et ce traitement est en règle bien toléré. Nous décrivons ici une complication inhabituelle associant un syndrome d’activation macrophagique et une hépatite granulomateuse. L’identification rapide de cette complication exceptionnelle et son traitement par des corticoïdes, des agents anti-tuberculeux et des immunoglobulines intra-veineuses ont contribué à une évolution favorable.

Case report

A 78-year-old man underwent one course of BCG intravesical instillations (Immucyst®) on July 12th, 2004 for low grade bladder carcinoma. No percutaneous BCG had been administered prior to this. The patient had a history of hypertension and dyslipidemia which was treated with nicardipine and fenofibrate respectively. A few hours after immunotherapy, he experienced fever with chills. Empiric treatment with ofloxacin and gentamicin was immediately started but was ineffective. Routine blood and urine cultures were negative and laboratory results were: aspartate aminotransferase (AST) 118 IU/L (N < 40), alanine aminotransferase (ALT) 80 IU/L (N < 50), alkaline phosphatase 142 IU/L (N < 130), GGT 298 IU/L (N < 70), albumin 30 g/L, C-reactive protein level 80 mg/L. Anti-tuberculous agents combining isoniazid 400 mg/d, rifampicin 600 mg/d and ethambutol 1 200 mg/d were started on July 24th without bacteriologic evidence. Chest X-ray and bronchoscopy were normal. Thoracic and abdominal scan revealed a ground-glass opacification of the lung bases and hepatosplenomegaly. A percutaneous liver biopsy showed several non-caseating epitheloid granulomas with giant cell reaction (figure 1a). Ziehl-Neelsen and auramine stainings showed no acid-fast bacilli and cultures were not performed. The patient’s clinical condition deteriorated with the appearance of jaundice leading to the interruption of anti-tuberculous therapy. The patient was referred to our hospital on August 6th, 2004 because of jaundice, persistent and unexplained high fever, anorexia, weight loss (66 kg on admission) and the appearance of pancytopenia. Laboratory findings showed total bilirubin level 166 µmol/L (N < 24) with conjugated bilirubin 123 µmol/L (N < 6), AST 93 IU/L, ALT 113 IU/L, GGT 97 IU/L, hemoglobin 9.3 g/dL, white blood cell count 2 900/mm$^3$ (83% neutrophils, 12% lymphocytes, 4% monocytes), platelet count 3 000/mm$^3$, triglyceride level 3.21 g/L, ferritin level 3 699 ng/mL (range 22-322) and factor V at 55%. Serological tests for parvovirus B19, hepatitis B and C, Epstein-Barr virus, cytomegalovirus and human immunodeficiency virus were negative. Bone marrow examination showed hemophagocytosis without atypical cells (figure 1b) and no microorganisms, including mycobacterium, grew after bone marrow culture.

The patient was treated with methylprednisolone 2 mg/kg/d for the first two weeks and 1 mg/kg/d the third week. Intravenous immunoglobulins 0.4 g/kg/d were also associated for the first five days. We decided to resume anti-tuberculous therapy (isoniazid 150 mg/d and ethambutol 600 mg/d) at a low dose because we were not convinced that anti-tuberculous agents were involved in the hepatic disorders. The patient’s condition gradually improved with a rapid increase in platelet count (214 000/mm$^3$) permitting his discharge at the beginning of September. At this time, total bilirubin level and ALT normalized and the results of other tests were as follows: alkaline phosphatase 145 IU/L, GGT 260 IU/L, AST 44 IU/L, ALT 93 IU/L, factor V 100%, hemoglobin 10.9 g/dL and white blood cell count 5 600/mm$^3$.

Discussion

This patient had granulomatous hepatitis diagnosed on liver biopsy associated with reactive hemophagocytosis. Hemo-
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Phagocytic syndrome was first suspected due to clinical (fever and hepatosplenomegaly) and biochemical (pancytopenia, high ferritin level and hypertriglyceridemia) results, and then confirmed by bone marrow aspiration. An effect of anti-tuberculous agents on biochemical abnormalities seems unlikely since pancytopenia and hepatitis improved when therapy was continued. Moreover, liver enzyme abnormalities were present before anti-tuberculous administration. Hemophagocytic syndrome was thought to be due to BCG, an immunomodulatory agent that is extensively used for treating superficial bladder carcinomas. Although the mechanism for the beneficial effects of BCG therapy remains unknown, this treatment reduces the rate of recurrence and improves the prognosis of these patients with a success rate of between 63 and 100% [4]. BCG therapy is considered to be safe. Most side effects occur during or shortly after instillation. Patients commonly experience minor symptoms such as bladder irritability, hematuria, low-grade fever or a flu-like syndrome thought to be a systemic cytokine reaction. Uncommon local major complications include granulomatous prostatitis, epididymo-orchitis, ureteral obstruction, bladder contracture and renal abscess. Systemic complications such as high-grade fever, pneumonia, articulargia, leucopenia and granulomatous hepatitis occur in less than 5% of cases. The incidence of granulomatous hepatitis is estimated at 0.7% and the association «granulomatous hepatitis and hemophagocytosis» has been reported on only one occasion [3]. Hemophagocytic syndrome is characterized by a fever that does not respond to antibiotics, hepatosplenomegaly, cytopenia, very high ferritin levels, and increased proliferation and activation of benign macrophages showing phagocytosis of blood cells in hematopoietic organs [5]. Hemophagocytic syndrome may be primary, due to genetic defects, or secondary due to malignant, auto-immune or infectious diseases [6]. The pathophysiological mechanism of hemophagocytic syndrome remains poorly understood, but uncontrolled T-lymphocyte activation causes increased Th-1 cytokine secretion promoting macrophage activation. In a recent study, jaundice and low factor V levels were reported in 60% and 34% of cases receiving BCG therapy, respectively [7]. Like in our patient who exhibited jaundice, coagulation disorders and low serum albumin levels, the clinical presentation may mimic liver failure. However, this reaction is thought to be a cytokine-mediated effect rather than actual liver failure, even if acute liver failure is sometimes observed. Compared to the case reported by Schleinitz et al. [3], our patient recovered from the hemophagocytic syndrome without using cytotoxic agents such as vinblastine. This favourable outcome was probably due to the prompt diagnosis and use of corticoids together with anti-tuberculous agents. In the present case, the hemophagocytic syndrome and granulomatous hepatitis was probably a result of hypersensitivity rather than BCG dissemination because no mycobacteria grew and the response to corticoid and anti-tuberculous agents was prompt. It was recently shown that the positive culture for mycobacteria (30%) in early-presentation disease (within 3 months after instillation) was rare compared to 67% of positive cultures in the late-presentation cases, i.e. cases which usually develop more than one year after the first instillation [8]. Although life-threatening, the hemophagocytic syndrome is difficult to diagnose when it develops in elderly ill patients. Pancytopenia may be due to many causes such as the direct suppressive effect of tuberculosis on hematopoietic tissue, hematological malignancy, adverse drug reactions, hypersplenism or vitamin deficiency. Moreover, diagnosis of the hemophagocytic syndrome may be underestimated due to false negative bone marrow examination results.

Optimal treatment of the hemophagocytic syndrome includes specific treatment of the underlying infectious disease, as in our case. A 6-month course of anti-tuberculous drugs is usually recommended except for pyrazinamide which is ineffective against M. bovis. The present case suggests that the prompt use of corticosteroids is beneficial for early cases of granulomatous hepatitis and the hemophagocytic syndrome. Because of the severity of the hemophagocytic syndrome, other therapies are often proposed, such as cytostatic drugs, cyclosporin A, plasmapheresis or intravenous immunoglobulins and anti-TNFα [6].

REFERENCES


