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.

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 was in good condition before the immunotherapy. He had a history of hypertension and dyslipidemia which was treated with nicardipin 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 epithelioid 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/mm³ (83% neutrophils, 12% lymphocytes, 4% monocytes), platelet count 3 000/mm², triglycerid 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/mm³) 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 113 IU/L, factor V 100%, hemoglobin 10.9 g/dL and white blood cell count 5 600/mm³.

Discussion

This patient had granulomatous hepatitis diagnosed on liver biopsy associated with reactive hemophagocytosis. Hemo-
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Early 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 tuberculous 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


Fig. 1 – a) Liver biopsy sample showing granulomatous hepatitis; b) bone marrow smear showing an activated macrophage with hemophagocytosis.

a) Biopsie hépatique montrant un granulome, b) prélèvement de moelle osseuse révélant un macrophage actif avec hémophagocytose.

