Bone marrow granulomas in mononucleosis

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Summary: Two patients with mononucleosis, one due to cytomegalovirus (CMV), and the other due to Epstein-Barr virus (EBV), presenting with high fever, malaise and hepatitis, had granulomas in the bone marrow but not in the liver. In patients who have unexplained fever, bone marrow granulomas may be a clue to CMV or EBV infection and need not initially raise the fear of prognostically more severe illness.

Introduction

We have studied two patients with initially unexplained fever, one due to cytomegalovirus (CMV) and the other to Epstein-Barr virus (EBV) infection, by means of liver and bone marrow biopsies. Whereas the liver biopsy had no specific features, granulomas with giant cells were found in the bone marrow in both cases.

Case reports

Case 1

A 25 year old female was admitted with a 10-day history of fever, headache, photophobia, sore throat, and anorexia. Infectious mononucleosis had been diagnosed 5 years previously. Physical examination revealed a temperature of 101.2°F, slightly inflamed pharynx and enlarged liver but no skin rashes or lymph node enlargement. The patient had a normal white blood cell count and a normal differential, but 10 days after admission she developed lymphocytosis (60%) with many atypical lymphocytes. She had elevated serum transaminase levels whereas her bilirubin and alkaline phosphatase were normal. A scintigram with technetium sulphur colloid, as well as an abdominal ultrasound, showed splenomegaly. ⁶⁷Ga scan demonstrated splenomegaly and increased uptake over the lower periaortic chain. Liver biopsy

showed Kupffer cell hyperplasia with focal aggregates but no classical granulomas. Bone marrow biopsy revealed granulomas, some with large multinucleated giant cells (Figure 1). Cultures and special stains for acid-fast bacteria and fungi were negative. CMV complement fixing antibody titre was 1/256 on the 14th day and 1/128 on the 34th day. CMV IgM immunofluorescent antibody titre was 1/64 (strongly positive) on the 37th day of illness. EBV serology revealed high titres of viral capsid antigen (VCA)-IgG (1/640), Epstein-Barr virus nuclear antigen (EBNA) (>1/80), and early antibody (EA) (1/20 or R type) but undetectable titre of VCA-IgM antibody (>1/10).

Figure 1 Section of bone marrow biopsy showing single discrete granuloma with giant cell. (Original magnification $\times 125$, haematoxylin and eosin stain.) Patient no. 1.

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These data were consistent with an acute CMV infection and reactivation of a persistent carrier state of EBV. The patient was febrile for 3 weeks, but 3 months later she was afebrile and well.

Case 2

A 51 year old male became ill with spiking fever (up to 104.6°F), chills, headaches, malaise, shortness of breath, jaundice and generalized macular rash. On examination he had palpable cervical lymph nodes, exudative pharyngitis, hepatomegaly, macular rash and scleral icterus. Peripheral white cell count was normal on admission but lymphocytosis (as high as 54%) and atypical lymphocytosis (33%) developed subsequently. Serum transaminases were highest on admission at 7–10 times normal: serum glutamic oxaloacetic transaminase (SGOT) of 460 IU/ml (normal <40 IU/ml) and serum glutamic pyruvic transaminase (SGPT) of 288 IU/ml (normal <40 IU/ml), whereas bilirubin and serum alkaline phosphatase reached peak levels (137 µmol/l and 54 IU/l) on the third day and ninth days after admission. CMV IgM titre was <1/16. On the 17th day after admission, the heterophile titre was 1/56 after absorption with guinea pig kidney and 1/14 after absorption with beef cells; on the 15th day the titres were 1/224 and 1/14 respectively. EBV serology revealed a primary virus infection since the specimen on the 19th day of illness had a high titre of VCA-IgM antibody (1/320), as well as a high VCA-IgG (1/640), but an undetectable EBNA titre (<1/2). On the 27th day of illness, the VCA-IgM titre decreased to 1/160 and the other titres remained the same. Liver biopsy showed normal lobular architecture but there was hyperplasia of Kupffer cells and infiltration of portal and periportal areas with mononuclear cells. No granulomas were present. The bone

Figure 2 Section of bone marrow clot showing two adjacent particles containing three discrete granulomas. (Original magnification $\times 125$, haematoxylin and eosin stain.) Patient no. 2.

marrow showed active haematopoiesis with M:E ratio of 3:1. Lymphoid cells and plasmacytes were increased to 15–20% of the cell population with plasma cells accounting for approximately 10%. Multiple small granulomas were scattered throughout the bone marrow clot, some containing multinucleated Langhans-type giant cells (Figure 2). The patient became afebrile and anicteric in 20 days.

Discussion

Our two patients with mononucleosis presented with unexplained fever, malaise and abnormal liver function. The initial white cell counts and differential counts did not indicate mononucleosis. In some cases of unexplained fever, liver granulomas have been useful clues to EBV^{1,2} or CMV^{3–5} mononucleosis. In our patients, however, the liver biopsies were non-specific whereas the bone marrow biopsies revealed scattered granulomas with multinucleated giant cells. The first patient had serological evidence of a recent CMV infection and of reactivation of a persistent EBV infection. The second patient had clearly an acute EBV infection and lacked evidence for other pertinent infections.

The multinucleated giant cells in granulomas are thought to result from the fusion of epithelioid cells derived from circulating mononuclear leucocytes. Viruses may facilitate cell fusion by altering cell surfaces. Cellular immunity frequently becomes depressed during acute CMV infection.^{3,7}

Granulomatous hepatitis may occur in many infections, including those due to viruses (CMV, EBV, influenza B), Chlamydiae (*C. trachomatis*), rickettsiae (Q-fever), bacteria (mycobacteria, spirochetes, *Brucella abortus* and *suis*, *Francisella tularensis*, *Listeria monocytogenes*), fungi (in particular *Histoplasma capsulatum*), parasites (*Toxoplasma gondii*, *Entamoeba histolytica*, and schistosomes), and as a reaction to foreign materials (beryllium). Of greater concern is its presence in systemic diseases such as sarcoidosis, Wegener's granulomatosis, and Hodgkin's lymphoma. Bone marrow granulomas have been described in most of the above conditions⁷ including infectious mononucleosis⁸ but not in CMV mononucleosis. The bone marrow granulomas in CMV or EBV infections are important to bear in mind in those cases of unexplained fever where their presence raises the suspicion of malignancy or other systemic disease and leads to ordering of expensive radioisotopic and radiographic tests as occurred in our patients.

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