Mixed cryoglobulinaemia and B-cell lymphoma in the absence of hepatitis C virus infection

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Abstract—Literary data favouring hepatitis C virus infection as an important aetiological agent in mixed cryoglobulinaemia and mixed cryoglobulinaemia-associated lymphoma have been reported. Hepatitis C virus infection does not explain, however, all cases. A case of hepaticic C negative mixed cryoglobulinaemia with B-cell lymphoma is presented and the possible role of hepatitis C virus in the aetiology of lymphoproliferative disorders and the geographical differences reported in the literature are discussed.

Key words: Mixed cryoglobulinaemia; B-cell lymphoma; hepatitis C virus infection.

INTRODUCTION

Mixed cryoglobulinaemia (MC) is a systemic vasculitis, due to the deposition of circulating immune complexes (mainly cryoglobulins and complement) in small and medium-sized blood vessels. MC is characterized by a typical clinical triad (purpura, weakness, arthralgias) and organ involvement: chronic hepatitis, glomerulonephritis, peripheral neuropathy, skin ulcers or diffuse vasculitis. It presents temperature-sensitive protein complexes. In type II MC, cryoglobulins are composed of a monoclonal rheumatoid factor (usually IgM kappa) against polyclonal IgG [1]. In some MC patients, a malignancy, i.e. B-cell non-Hodgkin’s lymphoma (NHL) or hepatocellular carcinoma, may also develop. Hepatitis C virus (HCV) infection has been found in a majority of patients with MC; positive HCV markers (91%) were significantly higher in MC patients than other rheumatic diseases (6.4%), namely systemic lupus, Sjögren’s syndrome, rheumatoid arthritis and systemic sclerosis, or healthy controls (1.2%). HCV seems to be their common aetiological agent; however, a combination of unknown co-factors

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(infectious, genetic, environmental) could be determinant for the appearance of different clinical patterns [2]. Silvestri et al. [3] investigated 470 patients with B-cell NHL. Global prevalence of HCV infection is 8.9% but was 95.4% among 22 patients with cryoglobulin production, compared with 4.6% prevalence among 448 without cryoglobulinaemia. Fifty per cent of HCV-related lymphomas were non-cryoglobulin producers [3]. In this paper, we report a case of a female patient with MC-associated B-cell NHL in the absence of HCV infection, focusing on the role of HCV and other aetiopathogenetic factors.

CASE REPORT

A 46-year-old female patient was admitted to our hospital because of arthralgia in both knees and ankles, Raynaud phenomenon, and purpuric lesions in the lower limbs for 3 years. A cutaneous biopsy performed 1 year before admission was reported as leukocytoclastic vasculitis. On this occasion, she was referred to our hospital with a new onset of symptoms. She had lost 6 kg in the last 3 months. On physical examination, her weight was 43 kg. She appeared pale and livedo reticularis was present in the legs and ankles. No lymphadenopathy was found. Purpuric lesions were observed in the ankles and oedema in the left knee and ankles. Laboratory tests disclosed haemoglobin 90 (normal range 80–140) g/l, MCV 86 (normal range 76–100) fl, platelet count 537 000 (normal range 150 000–400 000) per mm$^3$, and reticulocyte count 3.2%. White cell count was normal. Direct and indirect Coombs tests were negative. Serum IgG was 2.82 (normal range 8.00–15.00) g/l and rheumatoid factor was 21.2 (normal <15.0) kIU/l. Other biochemical tests were normal, as were serum IgA, IgM, ANA, anti-DNA, anti-scl70, ANCA, and urine electrophoresis. Cryoglobulins were positive. Component IgM kappa and polyclonal IgG were disclosed on cryoprecipitate. Serological tests for HIV and HCV (three different samples) were negative, as was HCV-RNA. Anti-HBs and anti-HBc were positive; HBsAg was negative. Serological tests for EBV (IgM, IgG and EBNA) were negative. CMV-IgM was negative and CMV-IgG positive. A synovial liquid study revealed normal synovial fluid. An electrocardiographic study was normal, as were colonoscopy, abdominal ultrasonographic study, thoracoabdominal CT scan, and chest, abdomen, knee, ankle, hand, foot, and pelvis X-ray films. A peripheral blood specimen was studied, showing atypical lymphocytes with evident nucleolus and nuclear incision. A bone marrow sample revealed 20% lymphocytes with a nuclear border and irregular cytoplasmic appearance. A bone marrow biopsy disclosed a low-grade non-Hodgkin’s lymphoma infiltration. The immunophenotype showed 26% lymphocytosis with 17% atypical B lymphocytes CD19+, CD5+, FMC7+, CD23+, CD22+, CD103–, CD25+, CD10– and CD11c– expressing surface kappa immunoglobulins. The patient was treated with six doses of CHOP chemotherapy and experienced complete clinical recovery.