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Reactive peripheral blood plasmacytosis in a patient with acute hepatitis A

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Abstract

Reactive plasmacytosis is a transient expansion of plasma cell progenitors and precursors. This rare condition has been reported mainly in infections and tumors. Here we describe a case of acute hepatitis A presenting with marked peripheral blood plasmacytosis. Plasma cells comprised 27.5% of mononuclear cells, and had the immunophenotype CD10-CD19⁺CD20-CD21-CD23-CD34-CD38⁺⁺HLA-DR⁺. Although the level of interleukin-6 was not increased, the presence of activated T cells with an inverted CD4/CD8 ratio and high levels of soluble interleukin-2 receptor and neopterin indicated a marked immune response to acute hepatitis A. The patient's plasma cells had almost disappeared from the blood by hospital day 16. This report may represent the first case of reactive peripheral blood plasmacytosis in acute hepatitis A.

1. Introduction

Reactive peripheral blood plasmacytosis is a transient expansion of benign polyclonal plasma cells in the circulation [1,2]. It is an uncommon clinical finding that has been associated with infections, autoimmune disorders, and neoplastic diseases [2]. Because of the rarity of the condition, the biology of reactive plasmacytosis remains undefined.

Acute hepatitis A is one of the most common infectious diseases [3]. Hepatitis A usually affects children without producing symptoms, but in adults it causes clinically apparent disease with jaundice. Extrahepatic, hematological manifestations of acute hepatitis A infection are rare [3], and plasmacytosis has not been described. In this report, we describe a patient with acute hepatitis A who developed extreme, transient peripheral blood plasmacytosis.

2. Case report

A 14-year-old Japanese male was referred to our hospital for evaluation of elevated liver enzymes. He had fever of 5 days' duration, malaise, and decreased appetite. Although his grandmother suffered from chronic hepatitis C infection, the patient had no history of liver disease. There was also no past history of allergic diseases and hypersensitivity to medicine. His liver was palpable 1.5 cm below the right subcostal margin, but the spleen was impalpable. He had no right upper quadrant tenderness. The rest of his physical examination was unremarkable. Laboratory studies revealed a WBC count of 3,500/ μ L, a hemoglobin level of 15.5 g/dL, and a platelet count of 13.1×10^6 / μ L. The differential leukocyte count included 50% neutrophils, 7% eosinophils, 1% basophils, 1% myelocytes, 31% lymphocytes, 2% atypical lymphocytes, and 8% monocytes. His liver enzymes were: aspartate aminotransferase (AST) 1,429 IU/L (normal 10-48); alanine aminotransferase (ALT) 2,308 IU/L (normal 3-50); total bilirubin (T-Bil) 2.4 mg/dL (normal 0.2-1.3) with direct fraction 1.4 mg/dL; alkaline phosphatase 750 IU/L (normal 108-324); γ -glutamyl transpeptidase 356 IU/L (normal 11-48); prothrombin time 15.6 seconds (normal 9.4-11.1); and hepaplastin test 40% (normal 84-158). A serum concentration of C-reactive protein (CRP) was 5.6 mg/dL. Immunoglobulin (Ig) levels were normal (IgG 1,260 mg/dL, IgA 188 mg/dL, IgM 182 mg/dL), and a monoclonal protein was not detected by serum protein electrophoresis. A hepatitis A IgM antibody test was positive (2.8; normal ≤ 0.8) on hospital day 2. Evaluation was negative for other infectious hepatitis including Epstein-Barr virus, cytomegalovirus, parvovirus B19, and viral hepatitis B and C.

As part of the clinical assessment, we performed fluorescence-activated cell sorting (FACS) analysis of peripheral blood lymphocytes [4]. As shown in Table 1, on hospital day 2 the ratio of CD4⁺ to CD8⁺ T cells was markedly inverted and the majority of CD4⁺ and CD8⁺ T cells expressed CD45R0, indicating an activated phenotype. Additionally, the level of soluble interleukin (IL)-2 receptor in the patient's serum was elevated at 3,980 IU/mL (normal 230-550). More importantly, an unusual mononuclear cell subset of CD19⁺CD20⁻ cells was significantly increased, with larger cells predominating (Figure 1A). Interestingly, CD19 expression was relatively low in these cells compared with CD19⁺CD20⁺ B cells. Multicolor FACS analysis revealed that they did not express CD10, CD21, CD23, CD33, or CD34, whereas expression of HLA-DR, surface IgM, and κ or λ chains was positive. In addition, CD38 was brightly expressed. These findings, together with observations of peripheral blood smears (Figure 1B), indicated they were plasma cells. Levels of plasma cytokines including IL-2, IL-6, IL-18, interferon- γ , and tumor necrosis factor- α were within normal limits on hospital day 2, except for neopterin (26 nmol/L; normal 2-8). Bone marrow aspirate on hospital day 3 showed normocellular marrow with 2.0% plasma cells and no evidence of malignancy.

The patient's fever diminished during the first few days in hospital, and his liver enzymes had almost returned to normal within 18 days of hospitalization. The percentages of CD19⁺CD20⁻ cells and activated T cells decreased with the course of the acute hepatitis A (Table 1).

Approval for the study was obtained from the Human Research Committee of Kanazawa University Graduate School of Medical Science, and informed consent was provided according to the Declaration of Helsinki.

3. Discussion

Plasma cells are terminally differentiated B cells specialized for antibody secretion. Following antigen activation in secondary lymphoid organs, memory B cells differentiate into plasmablasts that migrate into the bone marrow and finally develop into plasma cells [5]. Plasmablasts represent less than 0.1% of peripheral blood mononuclear cells, and plasma cells are usually undetectable in the peripheral circulation [6]. Although peripheral blood plasmacytosis is mostly a manifestation of plasma cell dyscrasias, reactive plasmacytosis has occasionally been described in a variety of conditions: tumors, autoimmune disorders, and infectious diseases including sepsis, primary infection and reactivation of Epstein-Barr virus, acute respiratory infections, parvovirus B19 infection, and dengue fever [1,2,7-11].

In this report, we describe an unusual case of acute hepatitis A presenting with reactive peripheral blood plasmacytosis. Reactive plasmacytosis is associated with increased levels of inflammatory cytokines, mainly IL-6, an important growth and survival factor for nonmalignant and malignant plasma cells [12]. Although serum levels of IL-6 have been reported to be significantly increased in patients with acute viral hepatitis A, B, and C [13], our patient showed no excess of IL-6. The rapid clearance of circulating IL-6 might have occurred in the patient. We also speculate that cytokines other than IL-6 could be involved in the development of plasmacytosis, as the IL-6 receptor subunit glycoprotein 130 is shared with receptors of IL-11, oncostatin M, leukemia inhibitory factor, and ciliary neutrophilic factor [14]. In particular, IL-11 has been detected as a growth factor of IL-6-dependent plasmacytoma [15], and IL-10 has

been reported to stimulate myeloma cells via oncostatin M [14]. However, other immunological markers such as lymphocyte subsets, soluble IL-2 receptor, and neopterin clearly indicated a marked systemic inflammatory response, which might have led to plasmacytosis and severe liver dysfunction in the patient. Although the patient was considered to have severe course of acute hepatitis A based on his liver parameters, the recovery process of the illness was unremarkable.

A number of changes in B-cell surface molecules have been identified upon plasma cell differentiation: CD19, CD20, CD21, CD22, and CD45 decrease in amount, whereas CD38 and CD138 increase [5]. Our FACS analysis of the patient's plasma cells is in good agreement with previous reports demonstrating that reactive plasmacytosis is a transient expansion of plasmablasts (plasma cell progenitors) and early plasma cells (plasma cell precursors) [1,2]. Plasmablasts are proliferating cells that are committed to becoming plasma cells, and early plasma cells are nondividing Ig-secreting cells committed to entering bone marrow and further maturing [2]. The surface phenotype of our patient's plasma cells was CD10⁻CD19⁺CD20⁻CD21⁻CD23⁻CD34⁻CD38⁺⁺HLA-DR⁺, a common phenotype among plasmablasts and early plasma cells, although we did not analyze CD138 expression, by which plasmablasts may be discriminated from early plasma cells [1]. Recent studies have shown that these cells are highly susceptible to apoptosis through their expression of high levels of CD95 but low levels of Bcl-2 [16]. Accelerated apoptosis might have been associated with the rapid and spontaneous elimination of CD19⁺CD20⁻ cells in the patient and the absence of accumulation of plasma cells in his bone marrow.

In summary, our results demonstrate that hepatitis A virus may be able to trigger an expansion of plasmablasts in vivo and provide important insights into the biology of reactive peripheral blood plasmacytosis.

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Table 1. Laboratory features of the patient.

	Hospital day			Normal range
	day 2	day 6	day 16	
Absolute blood count (/μL)				
WBC	4,900	5,100	4,500	4,500-11,000
Lymphocytes	1,862	2,052	1,994	1,500-3,000
Lymphocyte subsets (%)				
CD3 ⁺	73.2	70.8	66.2	69.5±4.6
CD4 ⁺	17.3	29.4	35.7	43.1±6.0
CD8 ⁺	48.8	36.7	26.9	22.0±5.4
CD16 ⁺	4.5	16.8	16.3	8.0±4.4
CD20 ⁺	2.8	7.5	8.0	11.2±3.5
TCRγδ ⁺	1.1	2.0	2.8	4.4±2.4
CD45R0 ⁺ in CD4 ⁺	66.8	62.9	57.9	28.7±9.2
CD45R0 ⁺ in CD8 ⁺	86.6	66.5	35.6	19.6±10.0
CD19 ⁺ CD20 ⁻ *	27.5 (685)	7.2 (114)	0.8 (15)	< 0.2
(absolute number, /μL)				
Other				
AST (IU/L)	1,000	208	41	10-48
ALT (IU/L)	2,149	988	155	3-50
T-Bil (mg/dL)	3.2	7.0	1.3	0.2-1.3
CRP (mg/dL)	NA	0.8	NA	< 0.3

*Percentage of cells defined in relation to total population of mononuclear cells. NA indicates not available.

Figure Legends

Figure 1. Characterization of the patient's plasma cells. A, FACS analysis of peripheral blood. A region of mononuclear cells was gated for the fluorescence analysis. Red indicates CD19⁺CD20⁻ cells. B, Peripheral blood smears. May-Grünwald-Giemsa staining, original magnification x 400. Arrow indicates plasmablasts.

Figure 1.

