Case Report

Famotidine-induced reactive plasmacytosis and generalized lymphadenopathy: a case report and review of the literature

Hiroaki Kitamura¹, Yasushi Kubota¹,², Noriyasu Fukushima¹, Tatsuo Ichinohe¹,⁵, Daisuke Hayasaka³, Kazuharu Kamachi¹, Mari Yoshihara¹, Hidekazu Itamura¹, Takashi Hisatomi³, Kazuo Wakayama⁴, Eisaburo Sueoka²,⁴, Shinya Kimura¹

¹Department of Internal Medicine, Faculty of Medicine, Saga University, Division of Hematology, Respiratory Medicine and Oncology, Japan; ²Department of Transfusion Medicine, Saga University Hospital, Japan; ³Department of Virology, Institute of Tropical Medicine, Nagasaki University, Japan; ⁴Department of Clinical Laboratory Medicine, Faculty of Medicine, Saga University, Japan; ⁵Department of Hematology and Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Japan

Received February 16, 2016; Accepted May 20, 2016; Epub July 1, 2016; Published July 15, 2016

Abstract: We report the case of a 53-year-old woman who presented with plasmacytosis, hypergammaglobulinemia, and multiple lymphadenopathy after upper respiratory infection. Although these symptoms mimicked those of plasma cell leukemia, serum immunoelectrophoresis, flow cytometry, and immunohistochemistry of bone marrow and an enlarged lymph node revealed polyclonal proliferation of plasma cells. In the absence of treatment, the plasmacytosis improved soon after ceasing the previously prescribed medications. A drug reaction was suspected as the cause of plasmacytosis because the patient had high serum IgE levels that decreased after discontinuation of the medications. A drug-induced lymphocyte stimulation test was performed for all of the drugs prescribed before admission: a positive result was only obtained for famotidine. The present case represents the first report of marked famotidine-associated plasmacytosis.

Keywords: Reactive plasmacytosis, hypergammaglobulinemia, lymphadenopathy, immunoglobulin E, famotidine, H2 blocker

Introduction

Reactive plasmacytosis is a rare condition that associates with infections, neoplastic conditions, inflammation, anemia, drug reactions, and autoimmune disorders [1-9]. The proliferation of reactive plasma cells is usually transient and disappears when the underlying disorders improve. However, recent reports have suggested that peripheral blood plasmacytosis is also a characteristic feature of life-threatening disorders such as dengue virus infection, including dengue hemorrhagic fever and dengue shock syndrome [10-13]. Therefore, when blood plasmacytosis is observed in primary care settings, a rapid and accurate differential diagnosis is needed.

The present report describes a patient who presented with extensive blood and bone marrow plasmacytosis and multiple lymphadenopathy. Although these symptoms resembled those of lymphoproliferative malignancy, immunohistochemical analysis and flow cytometry showed that the plasmacytosis was caused by non-neoplastic proliferation of polyclonal plasma cells, possibly associated with a reaction to the histamine H2-receptor antagonist famotidine.

Case report

A 53-year-old woman presenting with fever, fatigue, and cough was referred to our hospital. Her past medical history was unremarkable. Six days prior to admission, the patient visited her family physician because of dry cough. Despite the administration of antibiotic (cefcapene pivoxil), the patient’s symptoms were not resolved.

On admission, her body weight and height were 60 kg and 160 cm, respectively. The pyrexial (37.6°C) patient was normotensive (120/64...
mmHg), although her pulse rate was slightly elevated (106/min). Her room air pulse oximetry was normal. A physical examination revealed generalized lymphadenopathy with no palpable hepatosplenomegaly. A chest examination revealed no rales and regular heart sounds without murmurs or gallops. Laboratory tests on admission revealed a leukocyte count of 23.5×10⁹/L consisting of 54.5% neutrophils, 11% lymphocytes, 4.5% monocytes, 1% eosinophils, and 28% plasma cells that had a large and immature morphology (Figure 1A). The hemoglobin concentration was 127 g/L and the platelet count was 217×10⁹/L. Blood chemistry analysis revealed mild liver dysfunction [aspartate aminotransferase, 1.05 μkat/L (normal range 0.17-0.51); alanine aminotransferase, 0.67 μkat/L (0.17-0.68); lactate dehydrogenase, 9.59 μkat/L (1.7-3.4); and alkaline phosphatase, 8.02 μkat/L (0.5-2.0)] and a serum C-reactive protein concentration of 1178.12 nmol/L (normal range: 0.76-28.5). Bone marrow aspiration revealed a normocellular marrow with 33% plasma cells of small to medium size and a hyperbasophilic cytoplasm (Figure 1B). Serum protein electrophoresis exhibited a polyclonal pattern with increased amounts of IgM (4530 mg/L, normal range: 350-2200) and IgE (12,680 mg/L, normal range: 0-3600); the κ/λ free light-chain concentration ratio was normal (0.97). The patient had increased serum levels of soluble interleukin-2 receptor [sIL-2R; 2452 U/mL (normal range: 127-582)] and interleukin-6 [IL-6; 17.7 pg/mL (normal range: < 4.0)]. Serological tests for hepatitis B virus and hepatitis C virus were negative. Antibody tests for Epstein-Barr virus and cytomegalovirus showed patterns of past infection. The cell surface phenotype of the plasma cells on flow cytometry was CD38⁺CD138⁻ CD19⁺ CD56⁻ (Figure 1C). Chest radiography did not detect any abnormalities. Computed tomography (CT) indicated multiple lymphadenopathy that included the supraventricular fossa, the mediasti-
num, the bilateral hilum of lungs, and the para-aortic, mesenteric, and inguinal regions (Figure 2A, 2B). Neoplasms such as angioimmunoblastic T-cell lymphoma (AITL) were also suspected, and an inguinal lymph node biopsy was performed. Histological examination showed reactive lymphoid hyperplasia (Figure 2C-G). Monoclonal rearrangement of the T-cell receptor (TCR)-γ chain or immunoglobulin heavy chain (IgH) genes was not observed. On the basis of these findings, a clinical diagnosis of reactive plasmacytosis was made.

The marked increase in IgE levels suggested that the etiology of the plasmacytosis was a drug-induced reaction. Therefore, a drug-induced lymphocyte stimulation test (DLST) was performed for the drugs the patient had been prescribed with before admission, namely, loratadine, famotidine, cefcapene pivoxil hydrochloride hydrate, LAC-B granular powder N, ogikenchuto, by akkokanjinjinto, and saikokeishito. Only the test for famotidine was positive: the stimulation index was 2.2. The patient did not have anti-dengue IgM antibodies.

In the absence of additional treatment, the plasmacytosis of the patient improved soon after the prescribed medications were ceased. In parallel, the serum IgE and sIL-2R levels dropped and the multiple lymphadenopathy disappeared (Figure 3).

Discussion
The current patient presented with polyclonal peripheral blood plasmacytosis and multiple lymphadenopathy. The administration of the drugs with which the patient had been prescribed before admission was immediately stopped. Thereafter, differential diagnosis for the plasmacytosis and lymphadenopathy was performed. Monoclonal gammopathy, such as plasma cell leukemia, and lymphoproliferative disorders, such as multicentric Castleman's disease and AITL, were excluded. The plasmacytosis disappeared soon after cessation of the prescribed medications without any additional treatment. The DLST for famotidine was positive. The findings in our case strongly suggest that all presentations could be explained by a reaction to famotidine.
The presence of plasma cells in the peripheral blood is an uncommon condition that requires comprehensive diagnostic investigation. Reactive plasmacytosis is characterized by a transient increase in polyclonal plasma cells in the circulation. It has been reported to occur in association with infections, autoimmune disorders, neoplastic conditions, and drug reactions [2-9]. Atypical multinucleated plasma cells are occasionally observed. Although the present case was difficult to distinguish from plasma cell neoplasm on the basis of morphology, reactive plasmacytosis was diagnosed on the basis of the flow cytometry and immunoelectrophoresis results and the fact that the organ damage that typically associates with myeloma was lacking. The cell surface phenotype of plasma cells in patients with reactive plasmacytosis is CD56-negative and cyclin D1-negative [14]; our patient also exhibited this, as determined by flow cytometric analysis of the bone marrow plasma cells. Jego et al. reported that the cells in reactive plasmacytosis consist of CD20^+CD38^+CD45^+CD56^−CD138^− plasmablasts or CD20^−CD38^+CD45^+CD56^−CD138^+ early plasma cells [14]; in our patient, both cell populations were elevated. Furthermore, our patient had elevated serum levels of IL-6, which is a growth factor for plasmablasts [15, 16]. This suggests that IL-6 may have played a role in the development of the reactive plasmacytosis in our patient.

Reactive plasmacytosis usually disappears when the underlying disorders are treated or upon symptomatic therapy. However, several
reports have shown that steroid administration is effective for reactive plasmacytosis [17]. In the present case, the reactive plasmacytosis and generalized lymphadenopathy resolved within a few weeks after discontinuation of the medications prescribed by the patient’s family physician. These observations, combined with the elevated levels of IgE, indicated that the plasmacytosis was caused by a drug reaction. Indeed, DLSTs for all drugs prescribed before admission showed that famotidine may have caused the marked plasmacytosis and lymphadenopathy of the patients. While hematological side effects for famotidine, including neutropenia and thrombocytopenia, have been reported, albeit rarely [18-21], plasmacytosis associated with famotidine has never been reported previously. By contrast, previous studies have suggested that benign polyclonal plasmacytosis associates with dipyrone, streptokinase, intravenous immunoglobulin (IVIg) for Guillain-Barre syndrome, meropenem for infection in a patient with aplastic anemia, and methimazole for Graves’ disease [22-27]. Moreover, it has been reported recently that plasmacytosis often develops in patients with dengue virus infection [10-13]. The increasing popularity of overseas tourism indicates that a careful medical interview, including travel history, and laboratory testing for infectious diseases should also be performed when a patient presents with plasmacytosis.

In conclusion, the present report describes a case of reactive plasmacytosis and generalized lymphadenopathy after upper respiratory infection. To the best of our knowledge, this is the first case report of famotidine-induced plasmacytosis. When faced with a patient with unexplained plasmacytosis, clinicians should consider various causes, including drug reactions, as a differential diagnosis even if only frequently-used drugs such as H2 blockers are administered.

Acknowledgements

We thank the current members of the Division of Hematology and Oncology, Department of Internal Medicine, Saga University for helpful discussions.

Disclosure of conflict of interest

None.
Famotidine-induced reactive plasmacytosis


