Acquired C1-esterase inhibitor deficiency and positive lupus anticoagulant accompanied by splenic marginal zone B-cell lymphoma

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ABSTRACT

A 70-year-old woman complained of mild shortness of breath. Laboratory findings revealed pancytopenia, positive lupus anticoagulant and severe hypocomplementemia without antinuclear or anti-DNA antibodies. After the failure of prednisolone treatment, an acquired C1-esterase inhibitor (C1-INH) deficiency was diagnosed. There were no episodes of angioedema or deep vein thrombosis. Three months later, extreme splenomegaly was detected. Lymph node biopsy suggested splenic marginal zone B-cell lymphoma. Acquired C1-INH deficiency due to a lymphoproliferative disorder should be considered as a possible diagnosis for patients with severe hypocomplementemia.

Introduction

C1-esterase inhibitor (C1-INH) deficiency is a rare disorder, which usually causes episodes of angioedema, and is classified as either hereditary or acquired (1). The acquired form is thought to be associated with lymphoproliferative disorders (1) or autoimmune disorders such as systemic lupus erythematosus (SLE) (2).

Here, we report the first known case of acquired C1-INH deficiency and positive lupus anticoagulant (LAC) with splenic marginal zone B-cell lymphoma (SMZL).

Case report

A 70-year-old previously healthy woman was referred to our hospital in August 2005 with mild shortness of breath. The patient had never complained of Raynaud's phenomenon, xerostomia, xerophthalmia or arthralgia. Skin rash was not observed. There was no palpable lymphadenopathy. Laboratory data were as follows: hemoglobin, 7.3 g/dL; white blood cell count, 1800 /μL without atypical cells; platelet count, 11.8×10^4/μL; reticulocytes, 2.7%; lactate dehydrogenase (LDH), 224 IU/L. Hepatitis C virus antibody was negative. Bone marrow aspirate was normocellular without atypical cells. International normalized ratio (derived from the prothrombin time) and activated partial thromboplastin time were increased at 1.49 and 85.8 sec, respectively. C4 and CH_{50} levels were below detectable limits. C3, haptoglobin, immunoglobulin (Ig) G, IgA and IgM were within normal limits. Direct and indirect Coombs tests were negative. Assays did not detect rheumatoid factor, anti-nuclear antibody, anti-DNA, anti-RNP, anti-Sm, anti-Ro, anti-La or anti-cardiolipin/beta-2-glycoprotein-1 complex antibody. Although the patient did not suffer from deep vein thrombosis, LAC (based on diluted Russell's viper venom time) was positive at 1.61. These findings suggested a diagnosis of elderly-onset SLE with anti-phospholipid antibody syndrome. Treatment with oral prednisolone (PSL) 40 mg/day and aspirin 100 mg/day was started in mid-October 2005. The symptom was ameliorated at the beginning of November, but treatment was considered ineffective because of persistent pancytopenia and hypocomplementemia. The patient was found to have a low C1q level (2.7 mg/dL) and low C1-INH activity (47%). Consequently, her diagnosis was changed to acquired C1-INH deficiency. Although the cause of the C1-INH deficiency was unclear, PSL administration was terminated in late November 2005. No episodes of angioedema occurred. After termination of PSL administration, LAC was positive with a titer similar to that of the earlier test.

In December 2005, examination revealed enlargement of the spleen to 10 fingers below the left subcostal margin. Bone marrow contained aggregation nests consisting of atypical lymphocytes. In early February 2006, a biopsy specimen was obtained from a pretracheal lymph node, which was found to be positive for ^{18}F-fluorodeoxyglucose (^{18}F-FDG) accumulation on ^{18}F-FDG positron emission tomography (PET)/computed tomography (CT) (Fig. 1). ^{18}F-FDG-PET/CT also revealed strong ^{18}F-FDG accumulation in the spleen (Fig. 2). Lymph node histopathology showed vaguely nodular lesions comprising marginal zone proliferation consisting of neoplastic cells surrounding a germinal center. These cells were strongly positive for CD20 (Fig. 3), but negative for CD5, CD10,

CD23, CD43 and cyclin D1, which is consistent with SMZL. Serum LDH and beta-2-microglobulin levels were 256 IU/L and 6.7 mg/L, respectively. Serum immunoelectrophoresis using the Onchterlony method showed no monoclonal component. The international prognostic index score of lymphoma was 3, indicating intermediate-high risk. Because of the advanced clinical stage (IVA) and the mechanical discomfort caused by splenomegaly, the patient received 6 cycles of R-CHOP therapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone, from March to July 2006. The splenomegaly was markedly regressed following chemotherapy, and the levels of complement components and LAC recovered to their normal ranges.

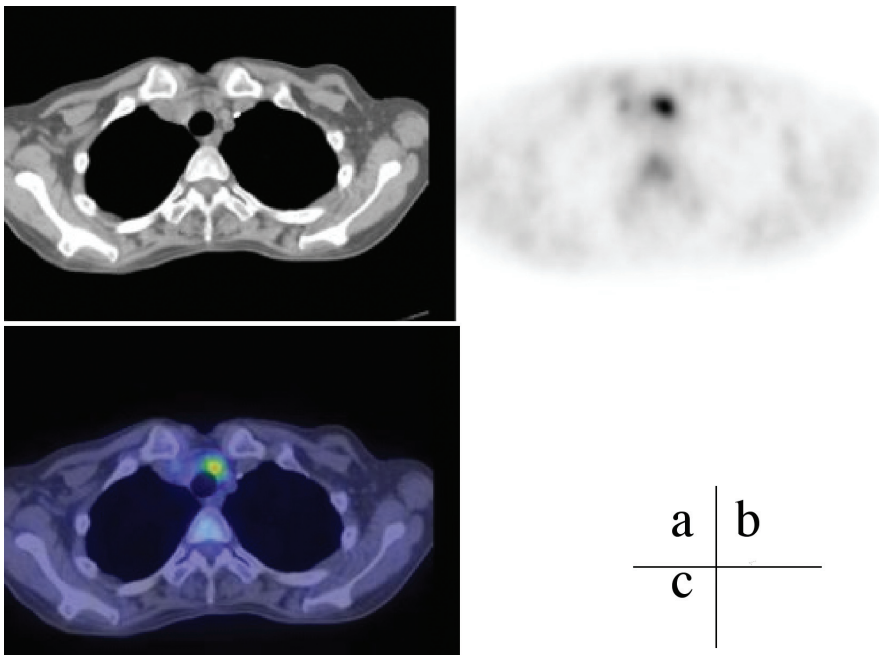

Fig. 1. CT (a), PET (b) and PET/CT (c) images of the chest. Although CT did not show a distinct enlarged lymph node, PET/CT revealed significant FDG accumulations in pretracheal lymphnode.

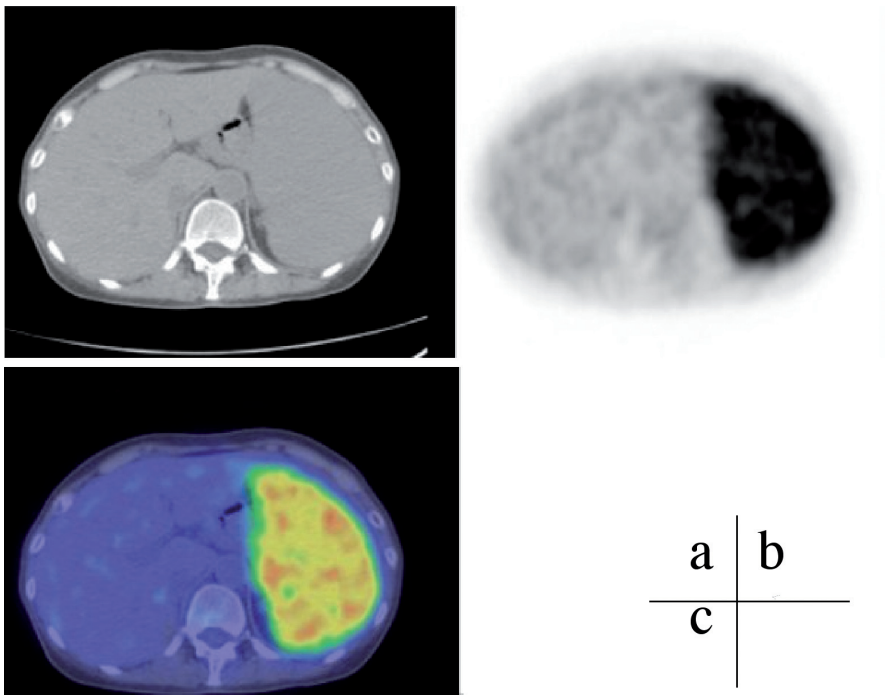

Fig. 2. CT (a), PET (b) and PET/CT (c) images of the abdomen. Strong FDG accumulations were detected in the greatly enlarged spleen. No accumulations in lymph nodes were observed.

Discussion

Acquired C1-INH deficiency, also known as acquired angioedema (AAE), is a rare syndrome with only about 150 reported cases (1). Although clinical manifestations of AAE are similar to those of hereditary C1-INH deficiency, also known as hereditary angioedema (HAE), AAE is characterized by elderly onset and a lack of family history. The serum C1q level is considered to be useful for distinguishing AAE from HAE (3). In the present case, the serum C1q level was significantly decreased, indicating AAE. Sub-classification of AAE is controversial; generally, AAE is divided into 2 pathogenic types (1, 3). In type-I AAE, an increase in consumption of available C1q molecules is induced by high levels of idiotype-anti-idiotype immune complexes produced by proliferating lymphocytes in underlying lymphoproliferative disorders (3-5). In type-II AAE, autoantibodies appear to inactivate C1-INH function (1), suggesting that immunosuppressive therapy such as PSL, which reduces autoantibody levels, would be effective against type-II AAE. In the present case, although assays for autoantibodies against C1q could not be performed, the patient was classified as type-I AAE because SMZL was present and PSL treatment was ineffective.

SMZL comprises less than 1% of non-Hodgkin's lymphoma, and its most frequent and characteristic manifestations are extreme splenomegaly and lymphocytosis (6). SMZL is also often accompanied by autoimmune disorders, such as autoimmune hemolytic anemia (AIHA) and Sjögren's syndrome (7, 8). Anti-phospholipid antibodies, such as anti-cardiolipin antibody and LAC, have only rarely been detected in SMZL patients (9, 10). However, anti-phospholipid antibodies appear to be reliable markers of SMZL activity (11). In the present case, AIHA and Sjögren's syndrome were not observed, but LAC was initially positive in repeated exam-

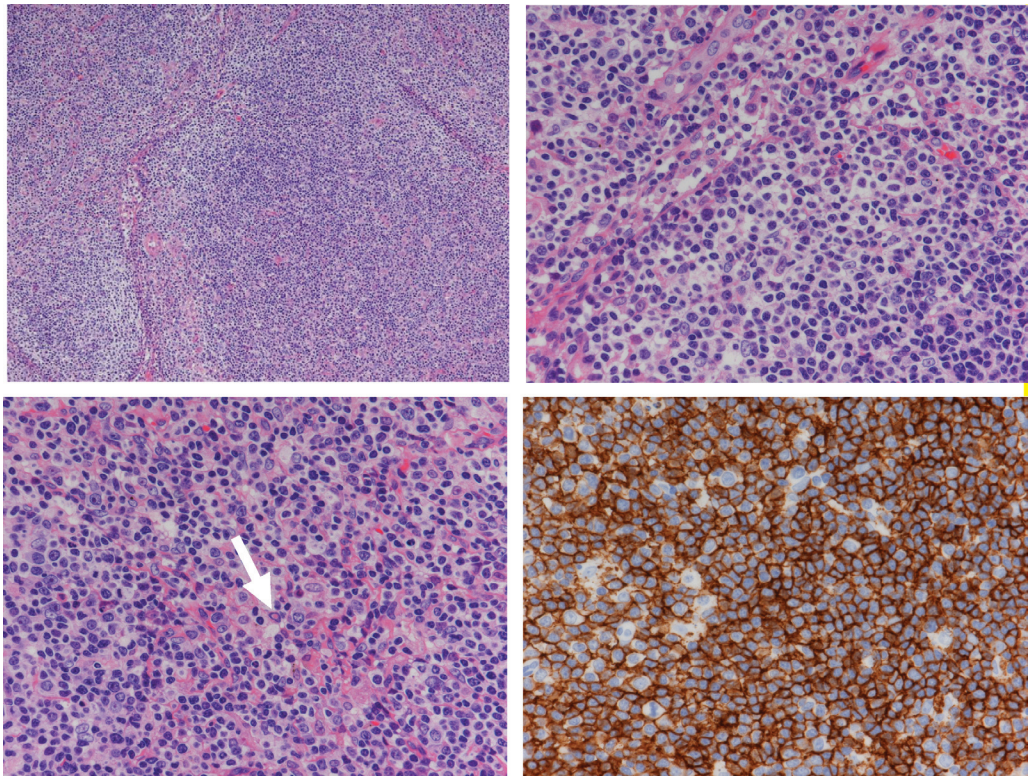

Fig. 3. Photomicrograph of the lymph node. Low- (**a**) and high-power (**b**, **c**) images and immunostaining for CD20 (**d**) suggested marginal zone B-cell lymphoma. Dutcher's body was occasionally observed (c, arrow).

inations and became negative after chemotherapy. Although it is unclear why the C1-INH deficiency coincided with positive LAC, both C1-INH deficiency and positive LAC may occur independently as a result of SMZL, as previously suggested (11). Moreover, it is unclear why angioedema symptoms did not occur in the present patient. Only 1 case of acquired C1-INH deficiency and positive LAC accompanied by germinal center lymphoma has been reported (12). To our knowledge, the present patient is the first reported case of SMZL coexisting with acquired C1-INH deficiency and positive LAC.

Similar to reports indicating that levels of complement components gradually recover following spontaneous remission of SMZL (4) and that C1-INH activity recovers after treatment of lymphoproliferative disorders in AAE cases (1), the levels of complement components in the present patient recovered after chemotherapy.

Although no episodes of angioedema were observed in the present case, the present findings suggest that acquired C1-INH deficiency based on a lymphoproliferative disorder should be considered as a possible diagnosis for patients with severe hypocomplementemia.

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