Successful Treatment of Catastrophic Antiphospholipid Antibody Syndrome Associated with MALT Lymphoma by Autologous Hematopoietic Stem Cell Transplantation

Satoko Oka¹, Kazuo Ono² and Masaharu Nohgawa¹

Abstract

A 37-year-old woman with extranodal marginal-zone lymphoma was admitted with a fever, hemiplegia, and severe dyspnea after chemotherapy. Catastrophic antiphospholipid antibody syndrome (CAPS) was suspected based on the histopathological confirmation of small-pulmonary vessel occlusion, evidence of the involvement of three organs, and elevated lupus anticoagulant assay results in a short time span. The patient responded to the initial treatment. One month later, the CAPS and lymphoma relapsed, and the patient underwent autologous hematopoietic stem cell transplantation. Complete remission of the lymphoma has been successfully maintained, and the condition of the patient has remained stable for two years with no further evidence of thrombosis.

Key words: catastrophic antiphospholipid antibody syndrome (CAPS), extranodal marginal zone lymphoma (MALT lymphoma), hematopoietic stem cell transplantation (HSCT)

(Intern Med 56: 1207-1212, 2017) (DOI: 10.2169/internalmedicine.56.7806)

Introduction

Catastrophic antiphospholipid antibody syndrome (CAPS) is a rare and potentially lethal variant of antiphospholipid syndrome (APS). APS is characterized by a constellation of arterial or venous thrombotic events, such as recurrent fatal loss, deep vein thromboses, and cerebrovascular events in the presence of antiphospholipid antibodies. CAPS is more fulminant than classic APS, typically manifesting over a few weeks as opposed to years. It is characterized by multiorgan system failure due to widespread microvascular thromboses, culminating in a mortality rate of 50% (1). A recent international consensus established the following definitive criteria for CAPS: the involvement of three or more organs, clinical manifestations within one week, histopathological evidence of macrovascular occlusion, and two positive antiphospholipid antibody titers at least six weeks apart. CAPS is suspected if the first three criteria are met despite positive serial titers not being available (2).

Immunomodulants, including rituximab, steroids, intravenous (i.v.) IgG, vincristine, and plasmapheresis, have been used to control the disease (3, 4). However, some patients develop more serious complications than others, with the failure of these therapies or relapse, and therefore require other forms of immunomodulation to control their disease. Hematopoietic stem cell transplantation (HSCT) may be considered if the disease is sufficiently severe to increase the risk of mortality or advanced and irreversible disability or if it is unresponsive to conventional treatments (5).

A relationship has been reported to exist between APS and carcinomas, in addition to antiphospholipid antibodies and hematological malignancies, e.g., lymphomas, lymphoblastic leukemia, monocyctic leukemia, and myelomonocytic leukemia (6). Malignancies themselves or procedures associated with the treatment of malignancies have been found to precipitate CAPS. The outcomes of patients with CAPS are worse in the presence of an additional malignancy than when no malignancy is present.

We herein report a patient with relapsing lymphoma and...
CAPS after R-CHOP therapy, even though R-CHOP therapy is strongly immunosuppressive. Although patients with extranodal marginal-zone lymphoma (MALT lymphoma) generally have an indolent clinical course, patients refractory to initial therapy or with advanced relapse or transformation to aggressive lymphoma have poor outcomes. We describe a case of relapsing CAPS and MALT lymphoma after chemotherapy that was successfully treated with autologous HSCT.

**Case Report**

A 37-year-old female with no history of thromboembolic complications visited our hospital for an evaluation of abnormal chest computed tomography (CT) findings in a routine physical examination (Fig. 1a and b). She had no symptoms, and although the initial laboratory data showed a normal platelet count and D-dimer levels, a prolonged partial thromboplastin time was noted, and she tested positive for IgG anti-cardiolipin (aCL) and anti-β2-glycoprotein (β2GP1) antibodies (Abs) (48.8 AU/mL [normal range: <10 AU/mL], and 18.2 U/mL [normal range: <3.5 U/mL], respectively). Her soluble interleukin 2 receptor (sIL2R) level was 1,130 U/mL (normal range: 145-519 U/mL). The patient underwent video-assisted thoracic surgery from S6 of the left lower lobe, and the diagnosis of MALT lymphoma was confirmed.

A microscopic examination revealed lymphoepithelial lesions characterized by diffuse infiltration of the lung parenchyma by small lymphocytes, monocytoid cells, and plasma cells (Fig. 2a). Immunohistochemically, lymphocytic cells showed lambda Ig light-chain restriction and positivity for CD20. A subsequent fluoro-deoxy-glucose (FDG)-positron emission tomography (PET)/CT scan revealed ground-glass opacities in the right lobe and intense FDG uptake in the mediastinal, right supraclavicular, and abdominal lymph nodes. No evidence of neoplastic infiltration was detected in the bone marrow. We categorized the Ann Arbor staging of MALT lymphoma as Stage IIIA with APS.

She was treated with standard anticoagulation therapy and maintained at an INR of 2-3. She received rituximab (375 mg/m², day 1) plus cyclophosphamide (750 mg/m², day 2), doxorubicin (50 mg/m², day 2), vincristine (1.4 mg/m², day 2), and prednisolone (50 mg/m², days 2 to 6) (R-CHOP) chemotherapy, and her chest CT findings (Fig. 1c and d) and sIL2R level (525 U/mL) markedly improved after 1 course of chemotherapy. After 4 courses of chemotherapy, she was admitted with a fever and hemiplegia. Brain magnetic resonance imaging (MRI) revealed acute infarction in the right anterior cerebral artery territory (Fig. 3). Within 6 hours, severe dyspnea with 90% SpO₂ in 10 L of oxygen developed, and the patient had to be intubated and ventilated. Chest radiography showed bilateral infiltration in the lungs (Fig. 4). She developed microangiopathic hemolytic anemia (MHA), including red cell fragmentation (schistocytes), hemolytic anemia, and thrombocytopenia, with her platelet count falling to 1.0×10⁹/L, and she had a negative
result for Coombs test. Further evidence of significant intravascular hemolysis included a lactate dehydrogenase (LDH) level of 513 U/L (normal range: 106-211 U/L) and decreased haptoglobin level of <10 mg/dL (normal range: 36-195 mg/dL). She was concomitantly noted to have a worsening renal function, with a creatinine level of 3.65 mg/dL (normal range: 0.4-0.8 mg/dL) and nephrotic-range proteinuria. Her ADAMTS13 level was not decreased (74%), and autoantibodies against ADAMTS13 were negative. ATIII and C3 were within normal limits [97% (normal range: 80-120%) and 69.9 mg/dL (normal range: 65-135 mg/dL)]. Sepsis and ARDS were suspected, and the i.v. administration of antibiotics was initiated. Blood, urine, stool, and tracheal fluid cultures were negative. Verotoxin was also negative. A transbronchial lung biopsy showed thromboses in small pulmonary vessels (Fig. 2b). Laboratory tests on admission showed that aCL and β2GP1 were markedly elevated (>120 AU/mL and 48.8 U/mL, respectively) (Fig. 5).
CAPS was suspected based on the histopathological confirmation of small-pulmonary-vessel occlusion, evidence of the involvement of three organs (brain, lungs, and kidneys), and elevated lupus anticoagulant assay results in a short time span, according to the classification criteria for CAPS (2). The patient was administered unfractionated heparin and plasmapheresis with the i.v. administration of a high dose of methylprednisolone at 1 g/day for 3 days. She initially responded to this therapy; her aCL and β2GP1 levels decreased (62 AU/mL and 25 U/mL, respectively), and she was consequently discharged following 4 weeks of treatment. However, one month later, she presented with generalized seizures and acute renal failure, and MRI revealed acute infarction in the parietal lobe with elevated aCL and β2GP1 levels (90 AU/mL and 37.2 U/mL, respectively) while she was receiving anticoagulation therapy and prednisolone. She was treated with low-molecular-weight heparin, i.v. IgG at 0.4 g/day for 5 days, and daily plasma exchange; subsequently, she recovered with decreases in her aCL and β2GP1 levels (62 AU/mL and 27.4 U/mL, respectively). However, CT showed enlarged abdominal lymph nodes (Fig. 6) with an elevated sIL2R level (860 U/mL), which indicated the deterioration of MALT lymphoma after chemotherapy. She was offered high-dose chemotherapy and autologous SCT for the treatment of lymphoma and CAPS. She was mobilized with G-CSF at 10 μg/kg and harvested when her WBC count was 10.0×10⁹/L.

In October 2014, she was conditioned with ranimustine (300 mg/m², day -6), etoposide (200 mg/m², days -5 to -2), cytarabine (200 mg/m², days -5 to -2), and melphalan (140 mg/m², day -1), followed by the infusion of CD34 at a total dose of 1.8×10⁶/kg. The complete remission of lymphoma was confirmed in PET/CT scans. The condition of the patient has since remained stable for two years with no further evidence of thrombosis.

**Discussion**

CAPS is a rare but serious complication of APS that has an extremely high mortality rate (50%) (1). The thrombotic manifestations of CAPS differ in their distribution from those of APS. In contrast to APS, in which the involvement of the deep veins of the extremities and pulmonary embolism predominate, patients with CAPS manifest small-vessel occlusion and most commonly present with abdominal pain.

---

**Figure 5.** Antiphospholipid Ab levels before and after the treatment.

**Figure 6.** Abdominal CT scan showing lymphadenopathies with the progression of lymphoma.
and intraabdominal thrombosis. The multiorgan involvement of CAPS typically manifests with renal failure (71%), respiratory failure (64%), and central nervous system involvement (62%) (7). According to the CAPS registry database, the disease is 3-fold more common in women than in men and is typically observed in patients around 40 years of age (6). In cases from the CAPS registry, a precipitating factor was noted in 53% of cases with infections (22%), with recent surgery (10%) being the most common factor. A total of 9% of patients reported in the CAPS registry had malignancies. Hematological malignancies were the most common (26%), followed by lung (17%) and colon (9%) cancers (6). In most CAPS patients with malignancies, the malignancies themselves or procedures associated with the treatment of malignancy were identified as precipitating factors of CAPS.

The management of CAPS is challenging for attending physicians, and an early diagnosis and aggressive therapies are essential to prevent these patients from succumbing to this potentially fatal condition. Immunomodulatory therapies are essential for the successful treatment of patients with CAPS. In addition to anticoagulant therapy and plasma exchange, prednisolone and i.v. IgG are commonly applied to the treatment of these patients, whereas cyclophosphamide, azathioprine, rituximab, and eculizumab are less frequently used. Rituximab is an anti-CD20 monoclonal antibody that has been successfully used in a limited number of APS patients with thrombocytopenia or autoimmune hemolytic anemia (4, 8). However, it was not possible to evaluate the antithrombotic effects of rituximab because rituximab-treated CAPS patients also received anticoagulants and multiple immunosuppressive agents. HSCT has been used in an attempt to control autoimmune diseases that respond poorly to conventional treatments or to readjust the immune balance. The success of HSCT in the treatment of some autoimmune diseases has encouraged physicians to extend its use to other autoimmune disorders, including APS (9, 10).

Relapse is rare in patients with CAPS, and the presence of schistocytes may be associated with the development of relapse (11). Recurrent arterial thrombosis appears to be more common than venous recurrence in patients with APS (12). In our case, the first attack was thrombosis in the cerebral artery and pulmonary and renal vessels, and the second attack was recurrent thrombosis in the cerebral artery.

We herein described a patient with relapsing lymphoma and CAPS after R-CHOP therapy, even though R-CHOP therapy is strongly immunosuppressive. MALT lymphoma improved after one course of R-CHOP therapy; however, the progression of lymphoma was noted after four courses of therapies, which may be related to the development of CAPS. Although we were unable to reach a histopathological diagnosis at the progression of lymphoma, histopathological transformation to aggressive lymphoma was suggested because of the progression of lymphoma after chemotherapies with the occurrence of CAPS. Patients with MALT lymphoma generally have an indolent clinical course, with a reported 5-year overall survival (OS) rate of 89% (13). Histopathological transformation to aggressive lymphoma occurs in 8% of MALT lymphoma cases and has been reported as a risk factor for an unfavorable outcome (13, 14). Patients who are refractory to initial therapy or demonstrate an advanced relapse or transformation to aggressive lymphoma have a shorter time to progression and OS than those who are responsive to therapy and stable. Although the optimum therapy has not yet been defined for patients with relapsed or refractory MALT lymphoma, recent findings on the use of high-dose therapy/autologous HSCT suggest durable remission and the possibility of a long-term disease-free survival (15, 16). Li et al. reported that high-dose therapy/autologous HSCT needs to be considered for patients who are rituximab-refractory and have disseminated lymphoma (16). Rituximab-containing chemotherapy was not effective in this case, and therefore high-dose therapy/autologous HSCT was needed. The indications for this treatment are therefore not the presence of autoimmune disease, but rather the presence of rituximab-refractory lymphoma.

Patients presenting with multiple thromboembolic events affecting diverse vascular beds are uncommon, and their management in the acute setting may be extremely difficult. There are numerous diagnostic challenges associated with thrombotic microangiopathy (TMA). Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC) are also manifestations of thrombocytopenia and hemolytic anemia, which thus makes differentiating CAPS from TTP/HUS/DIC difficult. An initial diagnostic evaluation of a patient presenting with multifocal or rapidly progressive thrombotic events includes a thorough history and physical examination, relevant imaging studies, and clinical laboratory data. History taking needs to cover the symptoms associated with acute thrombotic events, including timing, location, pace of progression, responses (if any) to initial therapies, prior thrombotic events, and a prior diagnosis of APS, aPL, or TTP. The underlying cause of TMA needs to be identified quickly, as the optimal treatment markedly varies depending on the diagnosis.

The survival rate of patients with CAPS is poor, and their outcomes are worse in the presence of an additional malignancy than in its absence. Miesbach reported that only 39% of CAPS patients with malignancies recovered (6). In the present case, CAPS developed after R-CHOP, which is strongly immunosuppressive, and the complete remission of lymphoma was achieved with the disappearance of antiphospholipid antibodies after HSCT. The disappearance of antiphospholipid antibodies after SCT supports the hypothesis that they are produced by lymphoma or the immune system as a response to tumor antigens.

In conclusion, CAPS needs to be considered in the differential diagnosis when encountering patients with malignancies, such as lymphoma, who present with multiorgan failure and the features of disseminated intravascular coagulation.
In addition, the decision to treat the condition using aggressive measures must not be delayed until all criteria are met.

The authors state that they have no Conflict of Interest (COI).

References

1. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 80: 355-377, 2001.
2. Asherson RA, Cervera R, de Groot PG, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 12: 530-534, 2003.
3. Miesbach W, Asherson RA, Cervera R, et al. The catastrophic antiphospholipid (Asherson’s) syndrome and malignancies. Autoimmun Rev 6: 94-97, 2006.
4. Rubenstein E, Arkfeld DG, Metyas S, Shinada S, Ehresmann S, Lieberman HA. Rituximab treatment for resistant antiphospholipid syndrome. J Rheumatol 33: 355-357, 2006.
5. Marmont AM. New horizons in the treatment of autoimmune diseases: immunosuppression and stem cell transplantation. Annu Rev Med 51: 115-134, 2000.
6. Miesbach W. Malignancies and catastrophic antiphospholipid syndrome. Clin Rev Allergy Immunol 36: 91-97, 2009.
7. Lim W. Antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program 2013: 675-680, 2013.
8. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 46: 1019-1027, 2002.
9. Olalla JI, Ortín M, Hermida G, et al. Disappearance of lupus anticoagulant after allogeneic bone marrow transplantation. Bone Marrow Transplant 23: 83-85, 1999.
10. Owaidah TM, Maghrabi K, Elkourori MA, Al Mohareeb F, Al Harthi A, Al Zahran H. Successful treatment of a case of catastrophic antiphospholipid syndrome with autologous BMT: case report and review of literature. Bone Marrow Transplant 46: 597-600, 2011.
11. Asherson RA, Espinosa G, Menahem S, et al. Relapsing catastrophic antiphospholipid syndrome: report of three cases. Semin Arthritis Rheum 37: 366-372, 2008.
12. Eisenberg R, Albert D. B-cell targeted therapies in rheumatoid arthritis and systemic lupus erythematosus. Nat Clin Pract Rheumatol 2: 20-27, 2006.
13. Maeshima AM, Taniguchi H, Toyoda K, et al. Clinicopathological features of histological transformation from extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue to diffuse large B-cell lymphoma: an analysis of 467 patients. Br J Haematol 174: 923-931, 2016.
14. Meyer AH, Stroux A, Lerch K, et al. Transformation and additional malignancies are leading risk factors for an adverse course of disease in marginal zone lymphoma. Ann Oncol 25: 210-215, 2014.
15. Brown JR, Gaudet G, Friedberg JW, et al. Autologous bone marrow transplantation for marginal zone non-Hodgkin’s lymphoma. Leuk Lymphoma 45: 315-320, 2004.
16. Li L, Bierman P, Vose J, Loberiza F, Armitage JO, Bociek RG. High-dose therapy/autologous hematopoietic stem cell transplantation in relapsed or refractory marginal zone non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 11: 253-256, 2011.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).