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Case Report

Mantle Cell Lymphoma Presented as Cryoglobulinemic Vasculitis

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Abstract

Mantle cell lymphoma (MCL) is an uncommon subtype of B-cell lymphoproliferative neoplasm which often presents as lymphadenopathy or organomegaly. Herein, we present the case of a 69-year-old male who developed the rapid onset of cyanotic digits and nose. Cryoglobulin was detected, and a skin biopsy showed occlusive vasculopathy, which suggested cryoglobulinemic vasculitis. A bone marrow biopsy confirmed the diagnosis of cyclin D1-negative, SOX11-positive MCL. He received systemic immunochemotherapy including bortezomib and rituximab, and his cryoglobulinemia completely resolved. In addition, his lymphoma remains in complete remission 2 years after the diagnosis.

Keywords: Bortezomib, cryoglobulinemia, cryoglobulinemic vasculitis, mantle cell lymphoma, SOX11, VR-CAP

Introduction

Mantle cell lymphoma (MCL) is a rare, aggressive subtype of B-cell lymphoma, affecting 3%–6% of patients with non-Hodgkin's lymphoma. Only around 70–80 of new cases are diagnosed in Taiwan annually, with a male predominance. Most cases present at an advanced stage, and extranodal involvement is frequent. Common presentations include generalized lymphadenopathy, hepatosplenomegaly, intestinal polyposis, and abnormal hemogram.[1] The diagnosis depends on a biopsy of the involved site and typical MCL cells expressing CD5, CD20, cyclin D1, and SOX11, but negative for CD10 and BCL6. A variant type of MCL has recently been identified, and its phenotype is negative for cyclin D1 but still positive for SOX11. This variant type of MCL has similar clinicopathologic features with typical MCL, but whether the treatment outcome is the same as that of cyclin D1-positive MCL remains unknown because previous clinical trials have included patients with cyclin D1 expression only.[2]

MCL is considered to be an incurable disease. Although an initial response is common, relapse eventually develops

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and most patients die of disease progression. Recent progress in first-line therapy for MCL includes the introduction of high-dose cytarabine and autologous stem cell transplantation (ASCT) for young fit patients and bendamustine/rituximab for older patients.[3] Recently, bortezomib combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) was shown to be superior to rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHOP) in a randomized Phase 3 trial.[4] VR-CAP is now considered to be a treatment option for patients ineligible for ASCT; however, real-world experience is still limited.

Cryoglobulinemia refers to the presence in the plasma of immunoglobulins that precipitate at a cold temperature and redissolve upon rewarming. This *in-vitro* phenomenon has been observed in a wide spectrum of hematologic, infectious, and immuno-rheumatologic disorders.[5] In a large retrospective etiologic study of cryoglobulinemia, 16 out of 443 (4%) patients had non-Hodgkin's lymphoma.[6] Most patients with cryoglobulinemia present with only mild orthostatic purpura, but in some severe cases, Raynaud's phenomenon with digital gangrene may develop.

Here, we report a patient with MCL who had an unusual presentation of severe cryoglobulinemic vasculitis and was treated with VR-CAP. Complete resolution of cryoglobulinemia and durable remission of lymphoma were achieved after treatment.

Case Report

A 69-year-old male farmer had a medical history of hypertension which was under control with valsartan and paroxysmal supraventricular tachycardia post ablation therapy. He visited the emergency room (ER) at a local hospital in April 2017 due to left flank pain for hours and then rapidly progressive dizziness, dyspnea, and chest tightness. Hypotension was noted at triage, and fluid resuscitation and empiric antibiotic treatment gradually stabilized his vital signs. However, distal limb cyanosis developed in the following days, and he was transferred to our hospital. A physical examination showed cyanosis of all the four distal limbs and his nose [Figure 1], with generalized lymphadenopathy and hepatosplenomegaly. A complete blood cell count showed the following values: hemoglobin, 12.5 g/dL; platelets, 72 × 10^9/L; and white blood cells, 27.6 × 10^9/L (abnormal lymphoid cells [20.0%], neutrophils [23.5%], lymphocytes [38.0%], and monocytes [2.5%]). A peripheral blood smear revealed medium-to-large lymphoma cells. An immunophenotypic study of a bone marrow sample was positive for CD5/CD20, CD19, surface lambda, and IgM and negative for CD3, CD4, CD7, CD8, and CD23. Immunohistochemical analysis of the bone marrow trephine biopsy was negative for cyclin D1 but positive for SOX11, confirming the diagnosis of MCL/leukemia.

Figure 1: Left foot and nose cyanosis as the initial presentation in our patient

Due to the clinical presentation of distal cyanosis, disseminated intravascular coagulation (DIC), drug-induced vasculitis, and cryoglobulinemia were considered. A meticulous history review excluded recent exposure to new medications, and his coagulation profile showed normal prothrombin time (11.9 s, reference range: 8–12 s), activated partial thromboplastin time (28.9 s, reference range: 24.6–33.8 s), and mild hypofibrinogenemia (139 mg/dL, reference range >180 mg/dL). His D-dimer level was elevated (20.55 mg/L, reference range: <0.55 mg/L), and the DIC diagnostic score was 4, which is not suggestive of overt DIC.[7] Plasma polyclonal IgG and IgM cryoglobulins were detected, and type III cryoglobulinemia was diagnosed. At the same time, his serum protein electrophoresis and immunofixation electrophoresis were negative for monoclonal gammopathy. Serum IgG and IgM levels were 2060 and 793 mg/dL, respectively, which were higher than the normal upper limits. His immunoglobulin A level was 288 mg/dL, which was within normal range. Serum free light chain kappa and lambda levels were 84.4 mg/L and 104.7 mg/L, respectively, with a normal ratio (0.81). A skin biopsy from a livedo reticular lesion in his right forearm revealed that the vessels were occluded by eosinophilic substances [Figure 2], which was compatible with cryoglobulinemic vasculitis.[5] Hepatitis B and C serology was negative. Antinuclear antibody and rheumatoid factor were negative. Blood cultures at the local hospital and our ER did not yield a microorganism.

High-dose methylprednisolone (160 mg/day) was administered when lymphoma was suspected, which slowed the progression of the cyanotic lesions. Systemic chemoimmunotherapy with VR-CAP was given after lymphoma workup which achieved rapid regression of circulating lymphoma cells, enlarged lymph nodes, and hepatosplenomegaly. The necrotic tissue was debrided, and the wound recovered well. Although he had febrile neutropenia after the first cycle of VR-CAP, he tolerated the following five cycles of therapy well. No rituximab maintenance was administered. Computed tomography showed

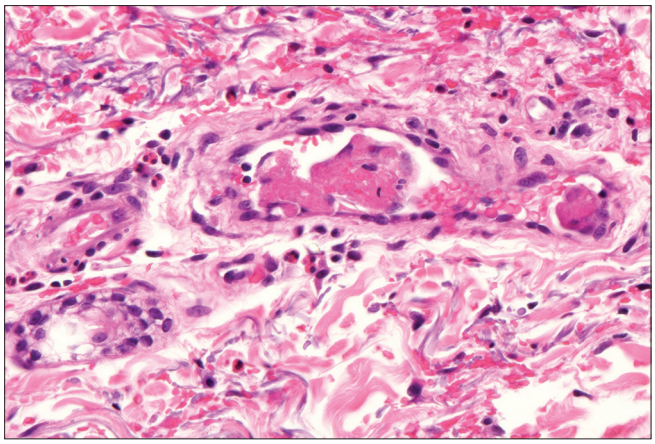

Figure 2: Eosinophilic substance in medium-sized vessels of a skin biopsy from the right forearm (×400)

a normal liver and spleen size with no enlarged lymph nodes. A bone marrow examination did not detect residual lymphoma cells. Plasma cryoglobulin could not be detected when he achieved a complete response and at 1 year of follow-up. His lymphoma remains in complete remission 24 months after VR-CAP initiation.

Discussion

We report the unique case of an MCL patient presenting with cyanosis of his nose and digits due to cryoglobulinemic vasculitis. Cryoglobulinemia has been reported to be associated with Waldenströme macroglobulinemia;[8] chronic lymphocytic leukemia;[9] and HCV-related, low-grade B-cell lymphomas.[5] However, to the best of our knowledge, there are no reports of MCL and cryoglobulinemia. Beyond cryoglobulinemic vasculitis, our patient also presented with lymphadenopathies, hepatosplenomegaly, and circulating lymphoma cells, which led to the correct initial diagnosis and allowed for prompt treatment. His cryoglobulinemia resolved after the lymphoma was in remission, and we hypothesize that it was an unusual paraneoplastic syndrome. Through an unknown mechanism, his MCL induced vigorous immune disturbances and resulted in severe cryoglobulinemic vasculitis, even though the patient claimed no cold exposure prior to this event.

Symptomatic cryoglobulinemia is an indicator to initiate therapy for low-grade lymphoma or Waldenströme macroglobulinemia,[8,9] and cryoglobulinemia had also shown to be an important prognostic factor of Waldenströme macroglobulinemia in a large retrospective study.[10] However, regarding other B-cell lymphomas, no relevant study has demonstrated the prognostic role of cryoglobulinemia due to its rarity.

MCL is an incurable disease, and the treatment goal is to achieve a longer remission and survival. VR-CAP showed better efficacy than traditional R-CHOP in the Lym-3002 study (progression-free survival, 24.7 months vs. 14.4 months, hazard ratio 0.63; $P < 0.001$), and it is currently considered to be an important treatment option for those ineligible for ASCT.[4] However, this trial included cyclin D1-positive MCL patients only; our case, who was cyclin D1-negative, also seemed to benefit from this novel therapy, although further studies are needed to confirm our results.

For patients with idiopathic cryoglobulinemia not related to hepatitis C, rituximab is the standard of care. Recently, a case report showed that a bortezomib-containing regimen successfully treated a patient with idiopathic cryoglobulinemic vasculitis.[11] In our case, both cryoglobulinemia and lymphoma regressed after VR-CAP treatment. The role of bortezomib in cryoglobulinemia with or without lymphoma warrants further investigations.

Conclusion

Cryoglobulinemic vasculitis can be an uncommon presentation of MCL. With the correct diagnosis and timely treatment, adequate disease control can be achieved and disease-associated sequelae can be avoided.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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