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Case Report

A Splenic Marginal Zone Lymphoma Case Presenting with Cyanosis, Spider Angiomas, and Polycythemia

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Abstract

Splenic marginal zone lymphoma (SMZL) is an indolent cancer classified among low-grade B-cell lymphomas in the World Health Organization (WHO) classification. The major characteristics of SMZL are splenomegaly, villous cytoplasmic protrusions of the lymphocytes in peripheral blood, anemia, and/or thrombocytopenia. The involvement of various organs, particularly the bone marrow or liver, can be frequently observed. SMZL has been reported to be associated with hepatitis C infection. The course of the disease is generally indolent, but aggressive behavior may be observed in a minority of patients. Here, we report a 43-year-old male hepatitis B virus carrier who presented with abdominal distension, multiple spider angiomas on the skin, and central cyanosis, leading to a diagnosis of SMZL.

Keywords: Splenic marginal zone lymphoma, cyanosis, spider angioma

Introduction

Splenic marginal zone lymphoma (SMZL) is a subtype of marginal zone lymphoma (MZL) that arises from marginal zone B cells present in the lymph nodes and extranodal tissues such as the spleen and mucosal lymphoid tissues. SMZL's major characteristics are splenomegaly, villous cytoplasmic protrusions of the lymphocytes in peripheral blood, anemia, and/or thrombocytopenia. Clinically, SMZL presents as an indolent and disseminated disease at diagnosis, with a specific clinical presentation that predominantly includes splenomegaly, followed by autoimmune manifestation in half of the patients. SMZL has been reported to be associated with hepatitis C infection. Here, we report a 43-year-old male hepatitis B virus carrier who presented with abdominal distension, multiple spider angiomas on the skin, and central cyanosis, leading to a diagnosis of SMZL.

Case Report

A 43-year-old male patient, working as a repairman, was referred to our hematology department because of progressive fatigue, abdominal distension, and widespread blue-purple lesions on the skin. He had been evaluated for his increased hemoglobin level elsewhere and underwent phlebotomy with a probable diagnosis of polycythemia. On admission, a history of abdominal distension and non-itching and painless skin lesions for at least 6 months was noted from the patient. Increasing fatigue and effort-induced restriction of daily activities appeared in time. He had no history of regular drug/medicine use. He reported to have smoked 20 pack-years until he quit smoking a year ago. His family history was unremarkable.

On admission, the patient's condition was attributed a moderate general status. He was conscious and cooperative. His blood pressure and pulse rate were 110/80 mmHg and 84 beats per minute, respectively. His limbs, tongue, earlobes, and fingernails were cyanotic. There were blue-purplish, spider web-like, non-pulsatile, discolored lesions on his scalp and body (Figure 1). Clubbing of the fingers was also noted. There were no peripheral lymphadenomegaly and venous distension. His abdominal examination was otherwise normal, except a non-tender palpable hepatomegaly 3 cm below the costal margin and an enlarged spleen.

The results of the initial blood tests were as follows: hemoglobin (Hb): 16.8 g/dL, hematocrit (Hct): 49.9%, MCV: 81.1 fL, white blood cells (WBC): 11,000/mm^3, and platelets (Plt): 129,000/mm^3. Peripheral blood smear included 54% neutrophils, 1.7% eosinophils, 36% lymphocytes, and 7.8% monocytes. CRP was 1.72 mg/dL (N: 0–5) and erythrocyte sedimentation rate was 1 mm/h. His biochemical values were normal. His respiratory function tests showed neither obstruction nor restriction. Arterial blood gas analysis was consistent with hypoxemia (pH: 7.40 mmHg, pCO_2: 28 mmHg, pO_2: 62.5 mmHg, and sO_2: 93%). The methemoglobin level was found to be normal

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Figure 1. Blue-purplish, spider web-like, non-pulsatile skin lesion on the face of the patient

(n=<1%). Hemoglobin electrophoresis excluded beta thalassemia and other variant hemoglobinopathies. An abdominal ultrasonography (USG) revealed an enlarged liver (151 mm craniocaudal), with normal parenchymal echo showing two intraparenchymal lesions of 11.6 mm and 9.3 mm, consistent with hemangiomas. The spleen was 129×98 mm. On splanchnic color Doppler ultrasonography, the diameters of his portal, splenic, and superior mesenteric veins were 18 mm, 8 mm, and 10 mm, respectively. The flow rate of the portal vein was 19 cm/sn (n=>11 cm/sn), and the hepatic artery RI was 0.75 (n=0.6–0.64). All of these findings were consistent with compensated portal hypertension. His viral serology was positive for Hbs Ag and negative for anti-HCV and anti-HIV. Endoscopic examination of the stomach revealed hiatal hernia and pangastritis. There was no varicose distension of gastric veins.

Considering the history of increased hemoglobin and venesection, the patient was tested and found to be negative for JAK-2-gene mutation. Serologic tests, including antinuclear antibody, anti ENA histone antibody, anti-Ds DNA, anti CCP, p-ANCA, and c-ANCA, were also negative. The findings of a skin punch biopsy from the aforementioned skin lesions were consistent with venous hemangioma. The von Hippel–Lindau syndrome was included in the differential diagnosis. No pathology could be identified on the cervical and lumbar magnetic resonance (MR) images. Genetic screening for the von–Hippel Lindau syndrome was planned but could not be performed because of financial reasons. Considering intermittent oral aphthous ulcerations, he was screened for Behçet's disease; the pathergy test was negative the ophthalmologic examination was normal.

Echocardiographic examination of the heart revealed right ventricular cavity expansion and normal left ventricular function. The erythropoietin (Epo) level of the patient was 182.99 mIU/mL (N: 2.95–18.5). To exclude the paraneoplastic increase of the Epo level, CT scans of the abdomen and chest were performed, which were unremarkable except for the presence of hepatosplenomegaly. As a result of the consultations, MR angiography and conventional venography of the abdomen was performed with the intent not to miss a vascular obstruction. The results were normal. The patient was discharged and advised to continue his further follow-up at the outpatient clinics.

Six months later, the patient was admitted to the emergency unit with acute abdominal pain. On physical examination, an enlarged, tender spleen extending to left groin was palpated. Abdominal USG confirmed the massive splenomegaly and excluded splenic infarction. Acute phase reactants were negative. His Hb level was 13.7 g/dL, decreased compared with prior levels. The repeated Epo level was found to be 241 mIU/mL, showing a significant increase. There was no significant change in the blood chemical analysis, including the lactate dehydrogenase (LDH) level. PET-CT imaging revealed FDG uptake in the spleen and bone marrow. A bone marrow biopsy was performed. It showed diffuse infiltration of B cell lymphoma. Splenectomy was offered as the treatment of choice, considering the compression symptoms caused by the enlarged spleen and the lack of extrasplenic nodal involvement. Pathological examination of the spleen was consistent with splenic marginal zone lymphoma. The hepatic wedge biopsy performed at the time of splenectomy showed low-grade lymphoma infiltrates in the portal tracts of the liver. Given the bone marrow and liver involvement, the patient was treated with six cycles of chemotherapy (R-CHOP, rituximab: 375 mg/m^2, D1; cyclophosphamide: 750 mg/m^2, D1; doxorubicin: 50 mg/m^2, D1; vincristine: 2 mg [total], D1; methylprednisolone: 80 mg [total], D1-5). Following the first cycle of treatment, the general status of the patient as well as his cyanotic appearance improved and the constitutional symptoms resolved. After completion of six cycles of chemotherapy, cyanosis and spider angiomas were almost totally regressed. The patient was in complete remission on his first control visit 3 months after the last dose of chemotherapy. Six months after the completion of chemotherapy, he was reported to have died because of a sudden gastrointestinal bleeding elsewhere. No details could be obtained.

Discussion

Marginal zone lymphoma is the common name for a tumor group originating from B lymphocytes that invade the micro-anatomic compartments of lymph nodes and extranodal tissues such as the spleen and mucosal lymphoid tissues. WHO defined three subgroups of MZL according to their characteristic molecular features and location: mucosa-associated lymphoid tissue (MALT), splenic MZL, and nodal MZL (1). SMZL is a rarely seen indolent lymphoma. It comprises less than 2% of all non-Hodgkin lymphomas and approximately 20% of MZLs (1, 2). Patients at diagnosis are generally 50 years of age or above. Females are more frequently affected (1). Villous protrusions of lymphocytes in peripheral blood may help for differential diagnosis (3-6). Splenomegaly is the hallmark of the disease. When it becomes massive, it is generally associated with cytopenias (1). Abnormal blood counts, particularly anemia and thrombocytopenia, are observed in most of the patients. Cytopenias are generally related to splenic sequestration rather than bone marrow involvement. Peripheral and intra-abdominal lymph node involvement is very rare; lymphocytosis can occasionally be present (1). Bone marrow and/or peripheral blood involvement are present in most of the cases. In total, 15% of the cases show peripheral blood involvement, which is represented by lymphocytes with villous cytoplasmic protrusions. This entity is called splenic lymphoma with villous lymphocytes (SLVL). However, it is controversial whether this is the leukemic equivalent SMZL or a subtype of the disease. By definition, patients with SLVL have more than 20% villous lymphocytes in the blood (1). B symptoms are rarely present in patients with SMZL (2). Fatigue and left upper quadrant pain are two of the most common complaints in patients with massive splenomegaly. LDH levels are generally normal. Our patient had normal levels of LDH, deepening anemia, and thrombocytopenia, which could be a result of massive splenomegaly as well as the bone

marrow involvement by lymphoma. A diagnosis of low-grade lymphoma was not considered at first sight because the predominant physical findings were cyanosis and angiomatous skin lesions.

Splenic marginal zone lymphoma is generally suspected in patients who present with lymphocytosis, cytopenias, or symptomatic massive splenomegaly. Liver involvement is seen in 90% of the SMZL patients, and nodulary infiltration in the portal area is observed (7). Immunophenotyping and morphological examination of the bone marrow and peripheral blood together with clinical presentation generally suggest the diagnosis of splenic MZL. To determine the villous lymphocytes in peripheral blood, a fresh smear should be prepared. To discriminate villous lymphocytes from those of hairy cell leukemia, immunophenotyping is required (6, 7). A typical finding is the expression of CD76. The other positive surface markers are CD19, CD20, CD22, FMC7, and CD79b (8, 9). Certain characteristic cytogenetic abnormalities such as 7q deletion may provide extra evidence for correct diagnosis (1, 9). In cases without bone marrow and peripheral blood involvement, diagnosis is generally made after splenectomy, as it was in our patient.

The diagnosis of SMZL in our patient was delayed and complicated by the unusual presentation of the disease. The first clue to the diagnosis was obtained through bone marrow biopsy, but the final diagnosis could only be made after splenectomy. Liver involvement was also confirmed via wedge biopsy. We were not able to show villous lymphocytes in peripheral blood. Immunophenotyping of peripheral blood using a flow cytometer was not performed.

Growing evidence suggests that MZL is associated with chronic antigenic stimulation by autoantigens and/or microbial pathogens. Chronic antigenic stimulation may lead to the malignant transformation of lymphoid cells. One of the best examples supporting this view is the association of Helicobacter pylori with gastric MALT lymphoma. Other chronic infections such as Borrelia burgdorferi, Campylobacter jejuni, and Chlamydia psittaci have been linked to cases of MZL, although their role in pathogenesis remains to be established (1). Hepatitis C virus (HCV) infection has also been associated with indolent lymphomas, including splenic MZL (10). In HCV (+) SMZL patients, antiviral treatment resulted in regression of the lymphoma. A study conducted in Italy reported that 83% of 255 SMZL patients were HCV positive (3). In another study conducted in Thailand, 41 of the 74 splenic lymphoma patients were reported to be HCV positive (11). Our patient was HCV negative but HBV positive. There are a few case reports speculating about the relationship between HBV and SMZL (12).

Patients without symptoms generally do not require treatment and may be followed without any treatment for years. In one study, none of the 32 SMZL patients required treatment, and the 5-year survival was found to be 88% (6). Approximately half of the patients, who do not need treatment initially, develop massive splenomegaly, causing symptoms of compression or symptomatic cytopenias, leading to treatment requirement (1, 2). Splenectomy is generally the treatment of choice in most of the patients. It generally provides a long-lasting disease-free period (13, 14). In recurrent or splenectomy-resistant cases, chemotherapy based on alkylating agents and purine analogues with or without rituximab has been reported to be effective. However, it has also been shown that chemotherapy has no impact on the recurrence rates, although it seems to increase the number of complete responses. In patients with HCV-associated splenic MZL, antiviral treatment with interferon (IFN)-alpha or IFN-alpha plus ribavirin has been reported to improve lymphocytosis and splenomegaly (14).

In our patient, we could not clearly determine the underlying cause of skin lesions and cyanosis, despite vigorous investigation. We therefore considered them to be of paraneoplastic origin. The depressed overall health status of the patient as well as the persistence of the skin lesions and cyanosis after the removal of the spleen made us to consider the response to splenectomy as "inadequate." Thus, chemotherapy was initiated. Improvement in cyanosis and venous hemangiomas on the skin indirectly confirmed our hypothesis about their paraneoplastic origin.

Conclusion

Lymphomas, particularly the low-grade lymphomas, have the potential to present with a wide spectrum of signs and symptoms. To the best of our knowledge, our case of SMZL was the first that presented with cyanosis. Molecular mechanisms that lead to cyanosis and spider angiomas could not be elucidated.

Informed Consent: Informed consent was not obtained because the patient was dead.

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