

Case Report

A 71-YEAR-OLD MAN PRESENTING WITH ANEMIA AND A SOLITARY SKIN LESION ASSOCIATED WITH PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA

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Abstract: A 71-year-old man with a solitary red lesion on his left arm, which initially thought being a hematoma, was admitted for inpatient evaluation of anemia, which after a positive direct Coombs test was qualified as autoimmune hemolytic anemia. The patient also presented with hoarseness and biopsies from the swelled nasopharynx and an enlarged right tonsil were obtained. Due to uncertain diagnosis and the patient's previous history of malignancy, (low grade lymphoproliferative lymphoma) skin and bone marrow biopsies were performed. Unfortunately, the patient's status rapidly deteriorated as a result of septic shock. The obtained skin, nasopharynx, and tonsil biopsies became available after the patient died and showed marginal zone lymphoma with no evidence of lymphoproliferative neoplasm in the bone marrow.

This case demonstrates the diagnostic complexity of nodal marginal zone lymphoma complicated by severe life-threatening autoimmune hemolytic anemia in an elderly patient with multimorbidity, which presents management challenges for health care providers.

Keywords: Autoimmune hemolytic anemia, therapy-resistant anemic syndrome, primary cutaneous marginal zone lymphoma, elderly, multimorbidity

INTRODUCTION We present a complex diagnostic case of an elderly patient with multimorbidity, which had initial disease manifestation as anemia, that was discovered on routine scheduled blood test. A case which initially thought to be an easy one for the medical management, but, put clinicians through numerous diagnostic and therapeutic challenges.

Primary cutaneous marginal zone lymphoma (PC-MZL) is a B-cell lymphoma is a relatively rare condition that arises in the skin. Clinical presentation includes solitary (80%) or numerous (20%) tumors that are 1–10 cm in diameter [1,5]. PC-MZL accounts for 20–40% of all primary cutaneous B-cell lymphoma in Western Countries, with an estimated incidence of 0.4 per 1,000,000 cases per year in the United States [1,3]. The diagnosis of PC-MZL may be

difficult, due to the rarity of the disease and variety of clinical presentations. Furthermore, the management of a patient after the diagnosis is complex and involves a dermatologist, hematologist, radiologist, and other specialists [7]. The aim of this case presentation is to describe the clinical and histological findings relevant to the diagnosis of PC-MZL complicated by refractory autoimmune hemolytic anemia (AIHA) in an elderly patient with multimorbidity.

CASE PRESENTATION

A 71-year-old Caucasian male was admitted to a hospital for management of anemia with a hemoglobin level of 7.1 g/dL.

The patient had been diagnosed with low grade lymphoproliferative lymphoma 5 years prior to the admission. At that time, he had presented with AIHA and a full body computerized tomography (CT) scan demonstrated a mass in the nasopharynx. Biopsy of this lesion established a diagnosis of the marginal zone lymphoma (MZL). He was treated with R-CHOP protocol (Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and achieved remission. In the two years

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prior to the present hospitalization, he was lost to regular hematological follow up.

The patients' medical history also included other comorbidities such as chronic atrial fibrillation treated with new oral anticoagulants (NOAC), severe peripheral vascular disease, post bilateral above knee amputation (pathology revealing severe atherosclerosis with no signs of thrombosis or vasculitis), chronic obstructive pulmonary disease as a result of heavy and active smoking, and essential hypertension.

In the emergency department, the patient reported dyspnea and dizziness. He denied having black or bloody stools.

The patient's vitals revealed a temperature of 36.4°C, blood pressure of 123/72 mmHg, a pulse of 100 beats per minute, respiratory rate of 14 breaths per minute and oxygen saturation of 96% in ambient air. He was alert and oriented. The conjunctivae were pale and the outer surface of the skin of the left shoulder displayed a 3.5 x 5 cm red-violet color lesion (oval-shaped tumor plaque with irregular outlines) (Figure 1).



Figure 1. Red cutaneous lesion on the patient's left shoulder.

A physical exam also revealed normal lung, heart, and bowel sounds. The abdomen was soft, nondistended, and not tender to palpation and no splenomegaly was present. A rectal examination revealed brown stool.

Blood tests obtained on admission showed a hemoglobin level of 6.7 g/dl with normal MCV, low reticulocyte index, elevated bilirubin, normal LDH, high haptoglobin, and

positive Coombs direct reaction (IgG). There was no evidence of iron, folic acid, or vitamin B12 deficiency and thyroid function was normal.

Throughout hospitalization the patient received 10 packed cell transfusions, but hemoglobin levels did not stabilize.

He underwent the following diagnostic evaluation:

- Gastroscopy and colonoscopy, which did not reveal a source of blood loss; both procedures were performed early at hospitalization because of subjective impression of "melena" on the second day of admission.
- FACS from peripheral blood was not diagnostic, as a low B cell count was found in the sample.
- Total body CT scan revealed no lymphadenopathy, space occupying lesions, or organomegaly.

The patient later underwent a bone marrow biopsy and a skin biopsy on the lesion, which were performed later due to the initial diagnosis of a hematoma.

While awaiting biopsy results, the patient's anemia was sustained, and he remained in the hospital due to blood transfusion dependency.

During this time the patient developed hoarseness as a new symptom. Examination by an ENT physician showed an enlarged right tonsil, tissue swelling in the right nasopharynx, and neck lymphadenopathy, which was not identified by CT scans of the neck. Subsequently, biopsies from the nasopharynx and tonsil were obtained.

Two days after the biopsies the patient deteriorated and developed septic shock and respiratory failure that required intubation. He was given broad spectrum antibiotics (IMIPINEM AND AMIKACIN) and was transferred to the ICU. A second total-body CT scan revealed bilateral lung consolidations and multiple new brain infarctions. As a result of these findings and the patient's history of atrial fibrillation (anticoagulation medication was discontinued on admission due to anemia) he underwent a transesophageal echocardiogram, which demonstrated a large patent foramen ovale, normal left ventricular contraction, and reduced right ventricular contraction.

Despite optimal antibiotic therapy, hemodynamic, and ventilatory support the patient died.

The following reports were obtained after the death of the patient: Skin biopsy histological and immunohistochemical

findings compatible with marginal zone lymphoma (Figure 2).

Tonsil and nasopharynx biopsies – low grade B-cell lymphoma (Figure 3).

presence of lymphoproliferative neoplasm, R-CHOP protocol treatment, 5-year medical history, multimorbidity, age, and absence of medical monitoring and management during last two years. The aging processes, as well as multimorbidity, increases the

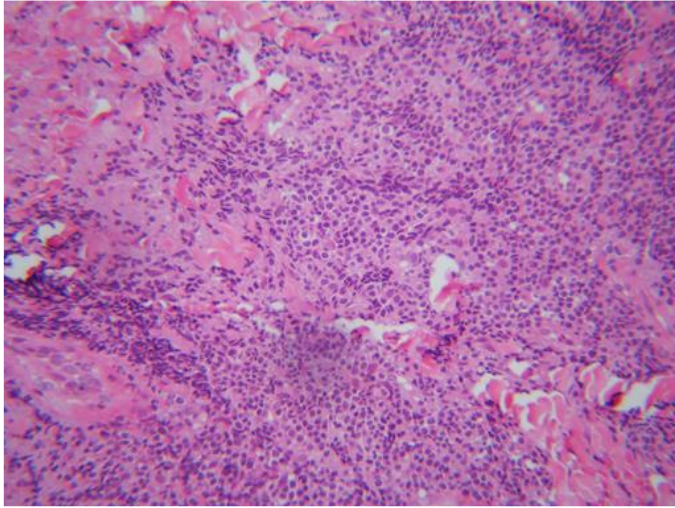


Figure 2. Patient's skin pathology. HE x400.

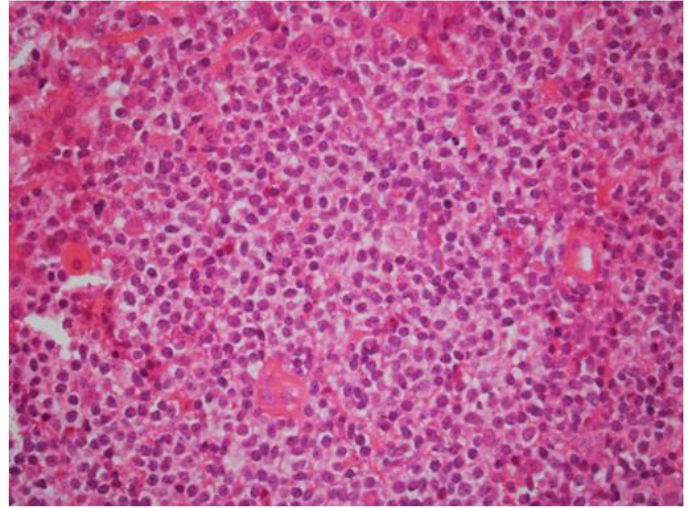


Figure 3. Patient's nasopharynx tissue pathology. HE x400.

Bone marrow – no definite evidence of bone marrow involvement by lymphoproliferative neoplasm. Additionally, myelodysplasia-like changes were probably secondary to chemotherapy in the past.

DISCUSSION The case showed a complexity of diagnostic and management challenges for health care providers taking care of an elderly patient with anemia and multimorbidity.

Firstly, the patient's medical history and lack of specific symptoms at presentation made for an extremely broad differential diagnosis on his admission to the hospital. Misleading first findings made it difficult to progress with the patient's examination and treatment.

It is currently estimated that the incidence of AIHA is 1.77 cases per 100,000 per year [2,4]. The clinical presentation and treatment of AIHA are influenced by many factors, including the type of AIHA, degree of hemolysis, underlying diseases, presence of multimorbidity, bone marrow compensatory abilities, and the presence of fibrosis and dyserythropoiesis [6,7]. This clinical case brings forth the possibility of therapy resistant AIHA on the basis of different burdened risk factors such as the

probability and severity of oxidative stress and eryptosis, (i.e., erythrocyte cell membrane changes) leading to RBC senescence and premature death [2,6].

Secondly, the occurrence of "melena" was misleading and lead to unnecessary invasive diagnostic procedures (gastroscopy and colonoscopy) while the patient did not have signs of iron deficiency. This resulted in loss of time, unnecessary expenses, and patient discomfort.

Thirdly, the cutaneous lesion was not immediately given proper attention and was at first explained as a hematoma, thus delaying tissue diagnosis.

Fourthly, the patient was treated with at least 10 blood transfusions because of unstable hemoglobin and symptomatic anemia. Blood transfusions were preceded by intravenous steroids and given through a filter due to the patient's Coombs positive reaction. Over time it became particularly challenging to establish venous access.

CONCLUSION

Currently, special diagnostic difficulties arise in the diagnosis of rare forms of lymphoproliferative diseases, especially PC-MZL of a complicated course with AIHA.

Close attention to the patient's medical history is imperative, especially in cases where elderly patients present with treatment-resistant anemic syndrome and multimorbidity. Our findings demonstrate the importance of prompt tissue biopsies in patients with a history of oncologic illnesses that present with cutaneous lesions.

Moreover, there are still many unanswered questions in this case:

1. Was the occurrence of hospital-acquired sepsis a result of relative immune deficiency because of relapsed lymphoma?
2. Were multiple brain infarcts on the patient's CT scan a result of embolism from cardiac origin after anticoagulation medications were discontinued upon admission?
3. Would it have been wise to reinstate the anticoagulation therapy after receiving the results of normal gastro-colonoscopy, although the reason for anemia was still not known?
4. And last, but not least, what was the primary cause of the patient's anemia? The bone marrow biopsy did not reveal definite evidence of bone marrow involvement by lymphoproliferative neoplasm. On the interdisciplinary discussion of this case, the hematologists assumed that the reason for the patient's anemia could be ineffective erythropoiesis and the appropriate therapy would have been erythropoietin. Unfortunately, the patient died before that treatment was implemented.
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