

## Case Report

### Splenic Marginal Zone Lymphoma complicated with cold autoimmune haemolytic anaemia

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#### Abstract

Splenic Marginal Zone Lymphoma (SMZL) is a distinct subtype of Marginal Zone Lymphoma (MZL) which is categorized under Non-Hodgkin Lymphoma. It is usually benign with the potential to transform into diffuse large B-cell lymphoma. Comorbid cold Autoimmune Haemolytic Anaemia (cAHA) is rare with SMZL. A case of a 53-year-old woman is presented here. She presented with fever and anaemic symptoms. Biochemical, radiological and histological investigations were done, and a diagnosis of SMZL complicated with cAHA was made.

#### Key words

Non-Hodgkin Lymphoma, Marginal zone lymphoma, Cold autoimmune haemolytic anaemia

#### Introduction

Of all non-Hodgkin lymphomas, MZL are ranked the second most common lymphomas comprising up to 7%.<sup>(1)</sup> There are three distinct subtypes of MZL: extranodal MZL, splenic MZL and nodal MZL. The natural history of MZL still remains poorly understood with the family history of lymphoma being an important risk factor. Other genetic and environmental risk factors include infectious agents and autoimmune disorders.

Autoimmune haemolytic anaemia can be categorized into three main types depending on the presence of antibodies: warm type, cold type, and mixed type. In cAHA, the antibodies are predominantly pentameric IgM subtype and bind to red blood cells at around 0 – 4° C. cAHA could be idiopathic or associated with autoimmune disorders, infections and B-cell pathologies.

#### Case presentation

A 53-year-old female patient presented with fever for one-week duration. She had pronounced anaemic

symptoms such as undue fatigue. She complained of abdominal discomfort. Other than that, no other focal symptoms of infection were present, and the systemic review was normal. She was a previously unevaluated patient with no alcohol or smoking history. The travel history was insignificant and there were no unsafe sexual behaviours, intravenous drug abuse nor history of blood transfusions. There was no family history suggestive of malignancies. She is a housewife with two children.

On physical examination, she was found to be pale and icteric. There was no cervical, axillary or inguinal lymphadenopathy. Abdominal examination revealed massive splenomegaly. Cardiovascular, respiratory and neurological examinations were unremarkable.

Considering the initial presentation of fever with gross splenomegaly, an initial suspicion of chronic malaria aroused. But microscopy for malarial parasite and malaria RDT were negative together with negative antibody test for hepatitis B and C. FBC showed Hb of 7.1 g/dL with an MCV of 113.5 fL, MCH – 41.5 pg, MCHC – 36.6 g/dL and a platelet count of  $71 \times 10^3$  suggestive of megaloblastic anaemia with thrombocytopenia. LDH was elevated – 586, total bilirubin – 35.9 and direct bilirubin – 11.9. TSH was 7.000 mIU/L.

Inflammatory markers CRP, ESR (130) were elevated. Mycoplasma antibody was negative. Blood culture was positive for skin commensal – coagulase negative *Staphylococcus* spp., sputum culture positive for coliform and urine culture showed heavy mixed growth.

Subsequently DAT IgG was weakly positive and C3d was positive – 3(+) and suggested cAHA probably in the presence of an infection. Together with that,

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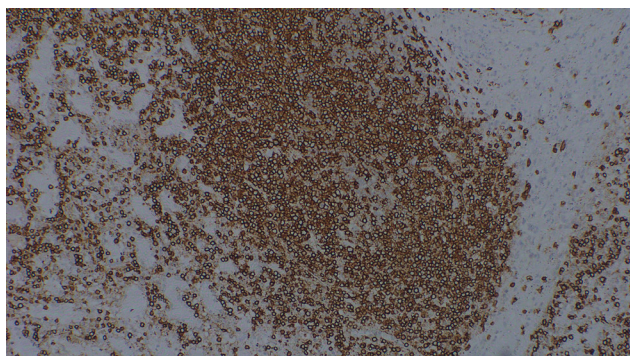


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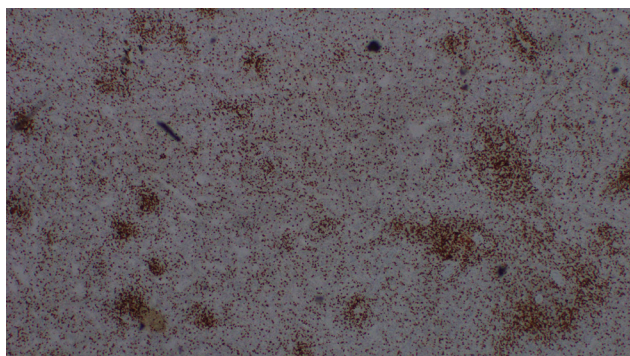
splenomegaly suggested lymphoma and CECT – chest, abdomen, pelvis was done, which did not show any lymph nodes.

With the worsening constitutional symptoms and febrile illness, as the initial investigations failed to help arrive at a definitive diagnosis, bone marrow biopsy followed by trephine biopsy and splenectomy with sample sent to histology, were done. BM aspiration report showed erythroid hyperplasia suggestive of chronic haemolysis. Trephine biopsy and splenectomy specimen histology findings are given below.

Trephine biopsy of the bone marrow showed a normal bony trabecular architecture seen with slightly hypercellular marrow spaces. Erythropoiesis is hypercellular. Granulopoiesis and megakaryopoiesis are normocellular. Diffuse interstitial, focal nodular and random focal and intrasinusoidal infiltration of bright CD20 positive small lymphoid cells with low proliferation index noted. Background CD3 positivity noted in the nodule.



*Figure 1 : CD20*



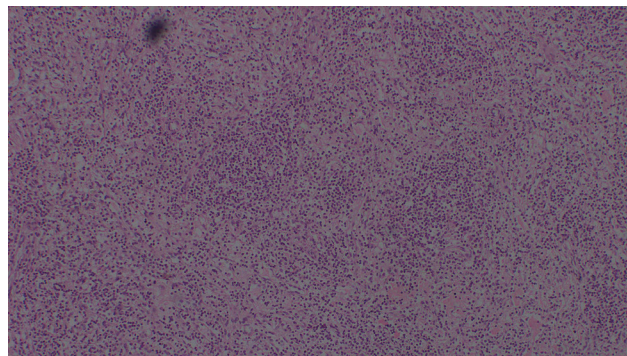
*Figure 2 : CD3*

Splenectomy specimen showed sections from the spleen show largely intact architecture. White pulp shows predominantly normal morphology with some

foci showing distorted foci. These foci show small lymphocytes with minimal nuclear atypia. Red pulp shows congestion. Immunohistochemistry – CD20, BC12 – Suspicious lymphoid cells are positive

CD3, CD10, CD23 – Suspicious lymphoid cells are negative.

Spleen histomorphology, immunohistochemical features and bone marrow findings are in favour of a SMZL. Hence, a diagnosis of SMZL complicated with cAHA was made.



*Figure 3 : H&E staining of splenic marginal zone lymphoma.*

Splenectomy was done with the aims of arriving at a definitive diagnosis and also as a treatment for massive splenomegaly.

After making the diagnosis, the patient was informed of the diagnosis, management options and the prognosis in the presence of his family members. She was then referred to oncology with rituximab infusions. Blood transfusions were given for symptomatic anaemia. High protein diet was prescribed from nutritionist. With the rituximab cycles, patient showed improvements symptomatically.

### **Discussion**

The exact pathophysiology of the SMZL remains obscure. Nearly 30% of patients are asymptomatic, and a watchful waiting approach is not detrimental.(1)

Cold agglutinin syndrome patients present with symptoms and signs of haemolytic anaemia. Investigations show an elevated reticulocyte count, increased serum LDH, elevated serum indirect bilirubin and decreased serum haptoglobin. DAT is also positive against C3d complement.(2)

Cytopenias are more frequent and commonly secondary

to hypersplenism in SMZL. Although, as in the case of cAHA, they can be immune mediated.(3)

It is very challenging to distinguish SMZL from other CD5- and CD10- negative benign B-cell lymphoproliferative. Spleen histology aids in arriving to a definitive diagnosis. But, in many patients, the characteristic morphology of peripheral blood lymphocytes can suggest a diagnosis of SMZL.(1)

Among all autoimmune haemolytic anaemia, cAHA accounts for around 25%.(2) In cAHA, the pentameric IgM binds to red blood cells at around 0–4° C. This leads to activation of complement system and deposition of C3b on RBC surface, ultimately resulting in erythrocyte destruction in the liver. On the surviving RBCs, the C3b is converted to C3d, causing a positive Direct Agglutination Test (DAT), which is a characteristic diagnostic feature of cAHA.(2)

It is difficult to comprehend the clinical course of lymphoma complicated with cAHA clearly, because of the diverse underlying diseases.

Regarding treatment for SMZL, there is no consensus, as there are no prospective randomized controlled trials. Treatment choices consist of active surveillance, splenectomy, or chemotherapy (commonly rituximab alone or in combination with some other cytotoxic agents).(2–4)

Considering cAHA, non-pharmacological management like avoidance of cold temperatures should be taken into account for all patients and might be adequate in patients with mild forms.

As the destruction of RBC is primarily known to happen in the liver, splenectomy is not recommended as a treatment in cold agglutinin syndrome.(2) Rituximab which is B-cell targeting antibody, is the gold standard to reduce the autoantibody production in patients with cold agglutinin disease.(2) According to a recent review

on rituximab as the treatment on AIHA secondary to non-Hodgkin lymphoma, it is suggested that it remains a valid therapeutic option, even though a considerable proportion of patients may relapse.(3,5) and the results of laboratory tests were as follows: hemoglobin (Hb Treatment of the underlying conditions remains as the mainstay of cold agglutinin syndrome therapy.(2)

## Conclusion

Splenic marginal zone lymphoma complicated with cold autoimmune haemolytic anaemia is an uncommon presentation.

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