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Case report

Splenic Marginal Zone Lymphoma (SMZL) In A Case of Autoimmune Hemolytic Anemia

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Abstract:
Splenic marginal zone lymphoma (SMZL) is a slow-growing (indolent) B-cell non-Hodgkin lymphoma (NHL).SMZL can affect persons of any age, however it is more prevalent in those who are around 50-60 years of age It is characterized by massive splenomegaly, moderate lymphocytosis with or without villous lymphocytes& rare involvement of peripheral lymph nodes. This is about a case of Splenic marginal zone lymphoma (SMZL) who presented with splenomegaly and lymphocytic predominance on peripheral blood smear. The diagnosis was further confirmed by immunohistochemistry of the bone marrow biopsy and bone marrow aspirate.
Keywords: *Aspirate, Biopsy, Immunohistochemistry, Lymphocytosis.*

Introduction:
Splenic marginal zone lymphoma (SMZL) comprises less than 2% of all lymphoid neoplasms[1]. Indolent B-cell lymphomas that derive from the marginal zone encompass three distinct entities: Extra-nodal MZ lymphoma of mucosa-associated lymphoid tissue (lymphoma), nodal MZL, and SMZL. SMZL is a B-cell neoplasm composed of small round lymphocytes that surround and replace the splenic white pulp germinal centers, efface the follicle mantle, and merge with a peripheral (marginal) zone of larger cells with pale cytoplasm, including scattered transformed blasts. Both small and larger cells infiltrate the red pulp. The median age at diagnosis of SMZL is 69 years. The overall age-adjusted incidence is 0.13/100,000 per year[2]. The 2016 World Health Organization classification has maintained the distinction between the three diseases according to the organ where it arises and introduced a new provisional category of splenic B-cell lymphoma/leukemia, unclassifiable encompassing, splenic diffuse red pulp small B-cell lymphoma (SDRPL), and hairy cell leukemia variant (HCL-V)[3]. Primary splenic small B-cell lymphomas mostly comprise the distinct entity of SMZL and the provisional category of splenic lymphoma/leukemia unclassifiable, mainly represented by the HCL-V and SDRPL. Patients present with massive splenomegaly and bone marrow involvement. Lymphadenopathy is very rare, and extra-nodal involvement is not there[4]. Lymphocytosis is commonly present, 25% of patients present with cytopenias, mostly due to hypersplenism[4].

Case Report:
A 48 year old male patient presented with complaints of breathlessness since 2 months, dry cough since 2 months, swelling in both the lower limbs since 2 months, easy fatigability, weakness, and dizziness since 4 months. Patient was known to have Acyanotic Congenital Heart Disease (Atrial Septal Defect – Ostium secundum type) diagnosed at 20 years of age. Patient was taking Tab. Torsemide (Loop Diuretic) 10mg once daily, Tab.Ramipril 1.25mg once daily which was prescribed by treating doctor and the same treatment was continued.

On Examination, Patient was conscious and oriented. Patient had severe pallor, but there was no lymphadenopathy seen. Patient was vitally stable, Pulse was 88/min, regular, BP was 110/70mmHg, SpO2 was 97% on room air and Respiratory rate was 20/min. On Cardiovascular examination, on auscultation, ejection systolic murmur was heard in pulmonary area, loud P2 heard with fixed splitting of second heart sound [findings of ASD]. On palpation patient had mild hepatomegaly and massive splenomegaly extending to the left lumbar region and around the umbilical region. Neurological examination was normal.

Lab Investigations showed Hemoglobin of 6.0g/dL, Total leukocyte count 38,600/µL with lymphocytes 92%, polymorphs 6%, eosinophils 2%, Platelet count of 180,000/µL, Reticulocyte count was 6.0%, Serum LDH was 1680U/L and Direct Coombs Test was positive.
ECG showed Right Bundle Branch Block which is suggestive of Ostium secundum type of ASD
Echocardiography shows ejection Fraction of 60%, Atrial Septal Defect of Ostium Secundum type (40mm) with Bidirectional shunt, dilated Right Atrium and Right Ventricle, Severe Tricuspid Regurgitation, Severe Pulmonary Artery Hypertension.
Bone marrow biopsy and aspiration was done and sample was taken from iliac crest.

The histopathological stained sections showed a hypercellular marrow with 60-70% cellularity. Flow cytometry performed on the aspirate revealed 18–20% of B cells which were positive for CD19 (Figure 1).

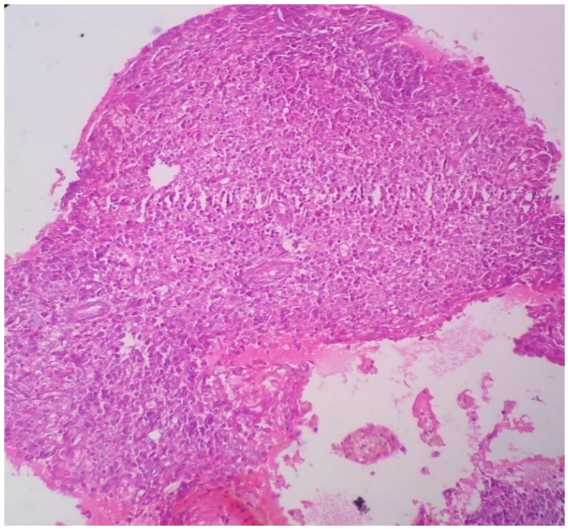

Figure.1 - Bone Marrow biopsy using Haematoxylin and Eosin stain under 40x magnification showing Large Nodular Lymphoid Aggregates.

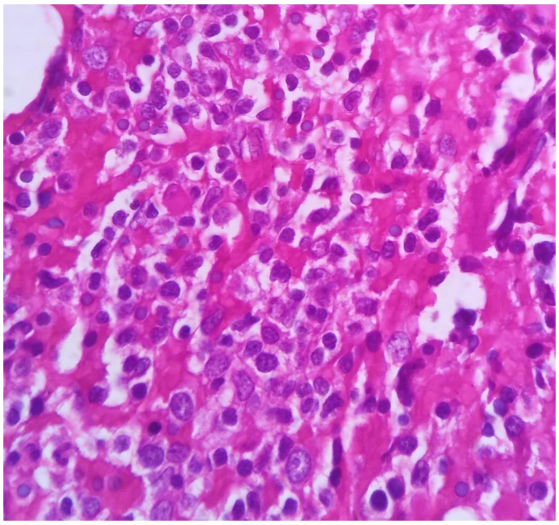

Figure.2 – Bone Marrow biopsy using Haematoxylin and Eosin stain under 400x magnification showing small centrocyte like cells with few plasma cells.

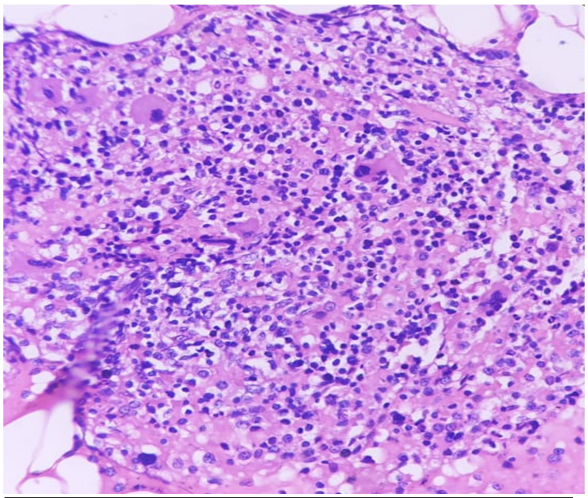

Figure.3 – Bone Marrow biopsy using Haematoxylin and Eosin stain under 100x magnification (HPF) showing numerous atypical lymphocytes.

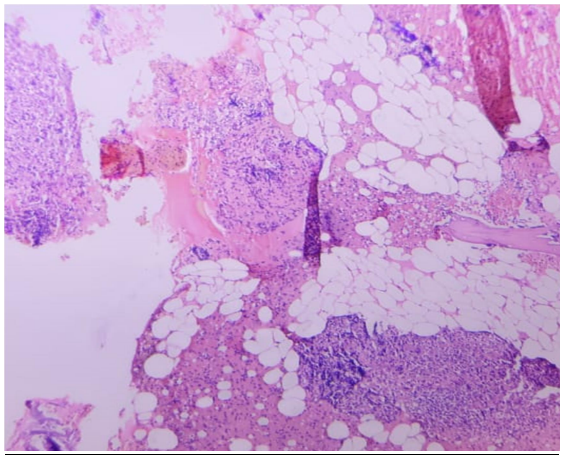

Figure.4 - Bone Marrow biopsy using Haematoxylin and Eosin stain under 40x magnification (LPF) showing islands of hematopoietic tissue.

IMMUNOHISTOCHEMISTRY:

Immunohistochemistry (IHC) Findings were positive for, CD11c, CD19, CD20 & FMC7 and negative for CD10, CD23, CD5, CD43 and CD25 & CD103.
In a case of autoimmune hemolytic anemia with a known case of congenital heart disease
(atrial septal defect), the outcomes of the clinical, blood investigations, bone marrow investigations, and Immunohistochemistry/flow cytometry studies confirmed the diagnosis of Splenic marginal zone lymphoma.

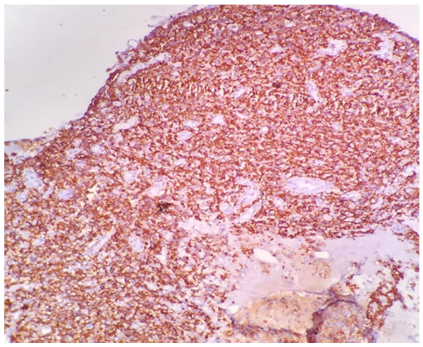

Figure.5 -Bone Marrow sample for Immunohistochemistry (IHC). Findings are positive for, CD11c, CD19, CD20 & FMC7

Flow cytometry	
CD 5	NEGATIVE
CD 10	NEGATIVE
CD 11c	**POSTIVE**
CD 19	**POSITIVE**
CD 20	**POSITIVE**
CD 23	NEGATIVE
CD 25	NEGATIVE
CD 43	NEGATIVE
FMC 7	**POSITIVE**
Kappa	**EQUIVOCAL**
Lambda	**EQUIVOCAL**
CD 103	NEGATIVE

INTERPRETATION: B cells, which have a significant predominance in lymphoid cells, are mixed with T cells (CD3+ and CD5+) that are CD20 positive. The B cells have a Ki 67 value of less than 10% and are Bcl2 positive but negative for CD5, CD43, CD10, and Cyclin D1, suggestive of Splenic Marginal Zone Lymphoma(SMZL).

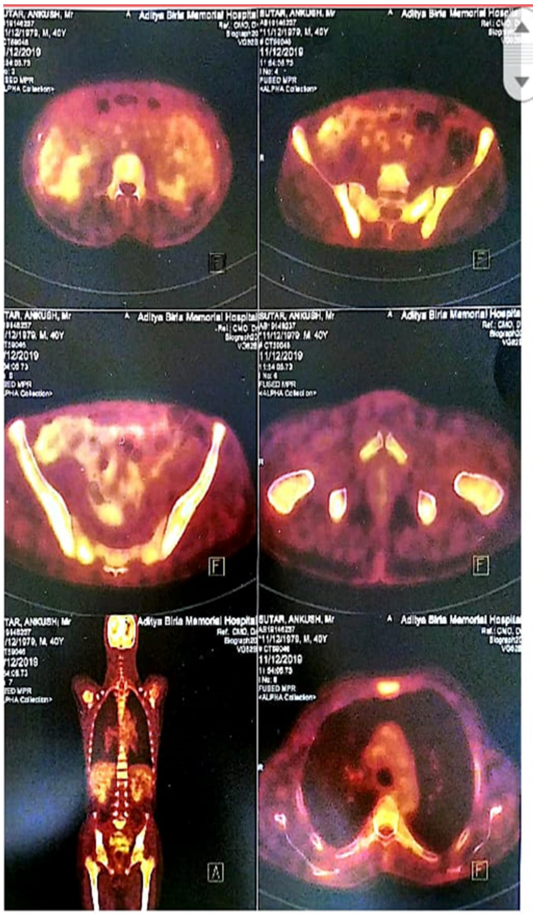

Figure-7 PET SCAN study reveals diffusely increased metabolic activity in the entire skeletal system with diffuse metabolic Activity in the Spleen is Consistent with Chronic Lymphoproliferative Disorder (figure 7)

Discussion:

Lymphomas can be divided into Hodgkin lymphomas and non-Hodgkin lymphomas. Non-Hodgkin lymphomas which are slow growing(low grade) are known as marginal zone lymphomas. They are called so because, they grow in a specific area called the marginal zone, which is located at the edge of healthy lymphoid tissues[5,6]. It accounts for less than 2% of all non-Hodgkin lymphoma and only 8.3% of all lymphoproliferative disorders involving the spleen[4].

Splenic Marginal Zone Lymphoma (SMZL) pathophysiology is still unclear. Although TP53 mutations and deletions, 7q deletions, and 3q gains are common in SMZL, their clinical significance and contribution to disease pathophysiology are still unknown[7]. The following mutations have been identified in SMZL and are thought to play a role in this process:

- Mutations in genes encoding Notch pathway components in up to 40 percent
- Mutations in genes encoding NF-KB pathway components in 35 to 40 percent
- KLF2 mutations in 20 to 40 percent
- MYD88 mutations in 3 to 15 percent
- CARD11 mutations in 5 to 10 percent
- KMT2D (previously known as MLL2) mutations in 7 percent

Involvement of Notch signalling in SMZL echoes the requirement for Notch2 in the development of marginal zone B cells[8].

Epidemiologic studies have identified an association between SMZL and infection with hepatitis C virus (HCV)[9] and Kaposi sarcoma-associated herpes virus (human herpesvirus type 8, HHV-8)[10].

Clinical Features:

The majority of patients present with splenomegaly, lymphocytosis, anemia, and thrombocytopenia. Patients are usually asymptomatic when diagnosed., a minority has symptoms related to splenomegaly (eg, early satiety, abdominal discomfort) or cytopenias (eg, bleeding). Rarely patients present with lymphocytosis as the sole marker of disease[1],Unlike most other non-Hodgkin lymphomas, lymphadenopathy and significant involvement of extralymphatic organs is uncommon[11]. Systemic B symptoms (eg, fever, weight loss and night sweats) are rare and should lead to a more detailed investigation for large cell transformation[12]. The cytopenias are most commonly due to hypersplenism, but may be immune mediated. Autoimmune diseases, including immune thrombocytopenia, cold agglutinin disease, autoimmune hemolytic anemia, antiphospholipid antibodies, acquired von Willebrand disease, and acquired C1-esterase inhibitor deficiency are associated with SMZL[13].

SMZL is usually suspected in an adult presenting with unexplained splenomegaly and lymphocytosis[14]. The diagnostic evaluation should include a hemogram with peripheral blood smear, histologic review of the bone marrow aspirate and biopsy, immunophenotypic analysis of the tumor cells, and measurement of serum immunoglobulins. Other studies that may be of use in determining the diagnosis include a histologic review of splenic tissue and genetic mutation analysis.
SMZL is diagnosed based on assessment of , bone marrow and spleen histology, tumor cell morphology, immunophenotype and cytogenetic analysis. The diagnosis of SMZL can most readily be made according to one of the following scenarios:

- The splenic histology and immunophenotypic pattern are consistent with SMZL, as described above.
- If splenic tissue is not available for histologic review, the diagnosis of SMZL can be made in a patient with splenomegaly and typical morphologic and immunophenotypic findings on blood smear and bone marrow biopsy.

Splenectomy and rituximab represent the most effective treatment strategies used so far. Splenectomy is considered as one of the first-line treatments for symptomatic patients with splenic marginal zone lymphoma (SMZL)[14].

- Choice of therapy — As described above, not all patients with SMZL require immediate therapy directed at the malignant cells. The management of asymptomatic patients is focused on the control of autoimmune complications (eg, cold agglutinin disease, immune thrombocytopenia, autoimmune hemolytic anemia,). Those with HCV infection are evaluated for antiviral therapy[15].
- For minimally or moderately symptomatic patients without HCV infection, we suggest single agent rituximab rather than splenectomy, rituximab plus chemotherapy, or the use of novel agents[16].
- For patients with severe local symptoms due to splenomegaly (eg, abdominal pain, early satiety with weight loss), we suggest splenectomy rather than other options. Splenectomy is not expected to benefit patients with disseminated nodal involvement outside of the splenic hilum or those with cytopenias due to extensive bone marrow involvement[17].
- Splenectomy is also indicated in patients with suspected large cell transformation within the spleen (eg, nodular splenic lesion with increased activity on PET).
- The combination of rituximab plus chemotherapy and novel agents (eg, ibrutinib) are usually reserved for patients with SMZL that has relapsed after or is refractory to treatment with single agent rituximab[18].

Conclusion:

The present case illustrates that it is possible to diagnose SMZL with clinical & haematological findings especially presence of massive splenomegaly with no lymphadenopathy. Bone marrow biopsies/aspirates and immunophenotypic findings will confirm the diagnosis The presence of classical cell morphology, with predominance of lymphocytosis along with flow cytometric immunophenotyping and typical nodular, interstitial, atypical lymphoid cells and intrasinusoidal pattern of infiltration by CD20- positive cells in the bone marrow is important clues to the diagnosis of SMZL ,which is pivotal in the management of the patient as this will guide the hemato-oncologist to a precise therapeutic intervention. Our patient received one cycle of rituximab, which was well tolerated with less adverse effects. After one month, patient came for second cycle of Rituximab and patient was stable and doing well.

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