Acta Scientific CANCER BIOLOGY (ISSN: 2582-4473)

Volume 8 Issue 1 January 2024

Case Report

"Unveiling the Uncommon" Splenic Marginal Zone Lymphoma - A Rare Case Report with Review of Literature

Aneez Ali[1], Gurpreet Kaur[2]*, Ankur Ahuja[3] and Y Uday[4]

[1]*Resident, Department of Pathology, Armed Forces Medical College, Pune, India*

[2]*Associate Professor, Department of Pathology, Armed Forces Medical College, Pune, India*

[3]*Professor, Department of Pathology, Armed Forces Medical College, Pune, India*

[4]*Professor, Department of Internal Medicine, Armed Forces Medical College, Pune, India*

***Corresponding Author:** Gurpreet Kaur, Associate Professor, Department of Pathology, Armed Forces Medical College, Pune, India.

DOI: 10.31080/ASCB.2024.08.0466

Received: December 11, 2023

Published: December 27, 2023

Abstract

Splenic marginal zone lymphoma (SMZL) is an extremely rare indolent non-Hodgkin lymphoma (NHL) comprising about 0.9% of all NHL, with a median age of presentation being 69 years. We present a case of splenic marginal zone lymphoma in an elderly male presented with easy fatiguability and massive splenomegaly of one year duration. His haemogram and peripheral blood smear showed anemia with absolute lymphocytosis, presence of villous lymphocytes and thrombocytopenia. Bone marrow biopsy revealed increased lymphocytes and a diffuse pattern of marrow involvement. CD19, CD20 were positive on IHC while CD5, CD23, CD10, CD103 and cyclin D were negative. Bone marrow aspirate flow cytometry showed a CD5, CD10, CD103 negative kappa restricted B Cell lymphoproliferative disorder and based on characteristic morphology the diagnosis of a SMZL was made and started on Rituximab and Bendamustine.

SMZL is a low grade B cell neoplasm composed of small lymphocytes that originate from the splenic white pulp germinal centers. Patients usually present with splenomegaly and usually there is no lymphadenopathy. SMZL pathogenesis involves antigen or super antigen stimulation and molecular deregulation of different genes including NOTCH2 and KLF2. Many studies believe that its pathogenesis may be closely related to 7q distortion. The prognosis of SMZL is overall favorable with a 5-year survival of approximately 70% and median survival > 10 years. Mainstay of treatment is chemotherapy and if indicated, splenectomy.

SMZL presents many unsolved questions, such as standard prognostic criteria and standard treatment because the clinical, immunophenotypic and genetic features of SMZL are different from other marginal zone lymphomas and hence case reports that clarify many issues are important in the clinical practice.

Keywords: Splenic Marginal Zone Lymphoma; Splenomegaly; Villous Lymphocytes; NOTCH2 Mutation; Indolent NHL

Introduction

Splenic marginal zone lymphomas (SMZL) are extremely rare comprising of less than 2% of all primary splenic lymphomas. SMZL is a mature B-cell neoplasm composed of small lymphocytes that arise from the spleen and are thought to be specifically derived from the marginal zone. There is a significant overlap in the clinical, laboratory and pathologic features. Presenting features usually relate to abdominal pain secondary to splenomegaly and in a few cases, patients may be asymptomatic with isolated splenomegaly. There is a lack of prospectively validated prognostic systems, treatment strategies & response criteria and hence more and more cases need to be reported to find consensus guidelines. Combined cytogenetic, biomolecular, splenic and bone marrow histopathology and Immunophenotyping correlation is needed for diagnosis SMZLs.

We hereby present a case of a 57 year old male with a SMZL who presented with splenomegaly and was thereafter put on Rituximab and Bendamustine where he responded adequately.

Case Presentation

Presenting concerns

57-year-old male with type 2 diabetes mellitus and hypertension presented with dragging left hypochondriac pain of one year duration. There was history of significant weight loss of 15 kg over 6-7 months however there was no history of fever or evening rise of temperature. On examination, vitals were stable, pallor was present. However there was no icterus, cyanosis, clubbing, lymphadenopathy or oedema. No skin lesions were seen. There was no sternal tenderness. The spleen was palpable within a length of 15 cm from subcostal margin in the left hypochondriac region. On imaging, spleen measured 23 cms in size with normal shape and echogenicity. With this, the possibilities of infections like Kala azar and malaria, chronic liver disease, hypersplenism, myeloproliferative neoplasms such as myelofibrosis and chronic lymphoproliferative disorders were considered.

His complete blood count showed anemia with Hb - 8.3 g/dL (normal Hb:13-17g/dl), total white blood cell count - 5300/mm^3 (normal WBC count: 4000-10000/mm^3) with relative lymphocytosis where absolute lymphocyte count being 2860/mm^3 and thrombocytopenia with platelet count of 90,000/mm^3(normal platelet count: 1.5 - 4.5 lakh/mm^3). The Leishman Giemsa stained peripheral blood smear showed characteristic villous lymphocytes having basophilic cytoplasm with short polar villi, round nuclei having condensed chromatin. Bone marrow aspirate was performed, which showed increase in lymphoid cells comprising of small lymphoid cells with scant cytoplasm and condensed nuclear chromatin with bipolar villous processes as shown in Figure 1 and 2.

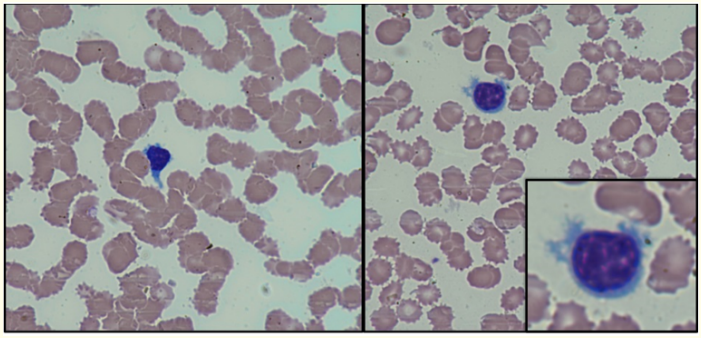

Figure 1: Peripheral blood showing characteristic villous lymphocytes having basophilic cytoplasm with short polar villi.

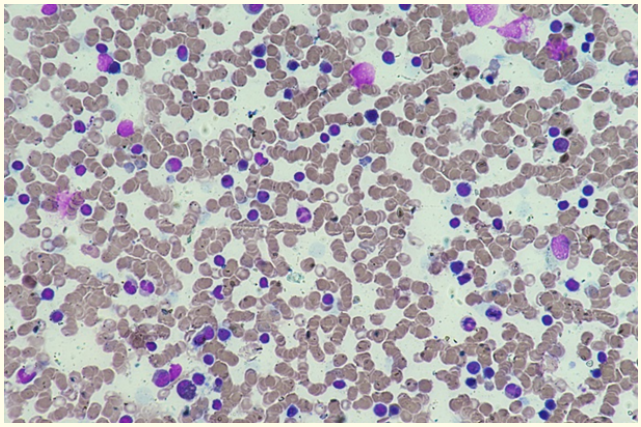

Figure 2: Bone marrow aspirate showing increase in lymphoid cells comprising of small lymphoid cells with scant cytoplasm and condensed nuclear chromatin with bipolar villous processes.

Peripheral blood smear and bone marrow aspirate was suggestive of a chronic lymphoproliferative disorder. Further on, bone marrow biopsy revealed a hypercellular marrow composed of sheets of lymphoid cells. On immunohistochemistry, these lymphoid cells were positive for CD19, CD20 and negative for CyclinD1, CD5, CD10, CD23 and CD3 (Figure 3).

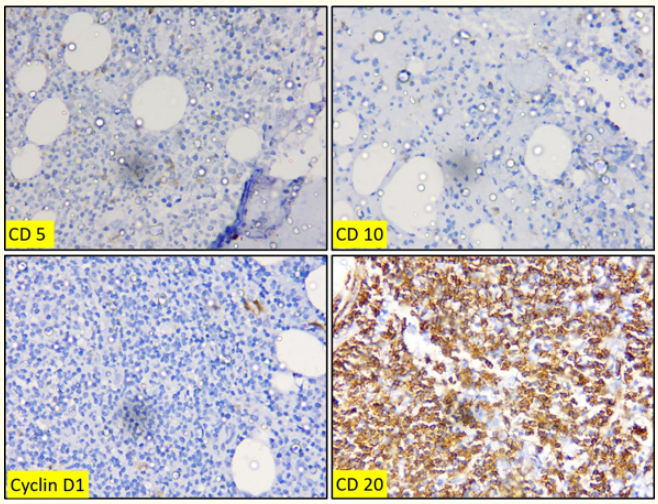

Figure 3: Immunohistochemistry showing positivity for CD20 and negative for CyclinD1, CD5 and CD10.

Multiparametric flow cytometry was done which showed 50.86% atypical lymphoid cells and these cells showed a bright expression for CD45, CD19, CD23, FMC7, CD200, moderate CD11c expression, bright dim CD25 and kappa restriction was seen (Figure 4). These cells were negative for CD5, CD10, CD25 and CD103. Based on the presence of polar villous lymphocytes and the immunophenotyping of a CD5 and CD10 negative, kappa restricted B cell lymphoproliferative disorder likely SMZL was considered. Cytogenetic analysis was essentially normal.

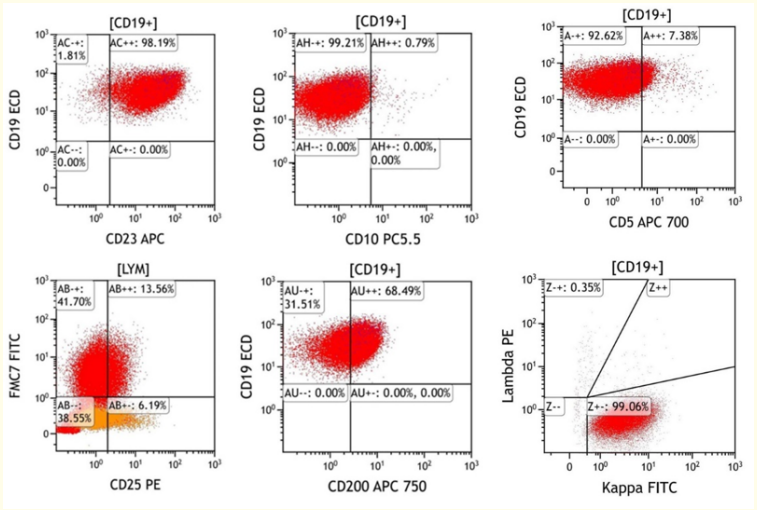

Figure 4: Flow cytometry plot showing a bright expression for CD19, FMC7, CD200 and bright dim CD25 and kappa restriction, negative CD5, CD10.

Laboratory study results showed elevated blood sugar levels (Fasting/postprandial: 204/225 mg/dL), but the other serum biochemistry results were within normal limits. Anti-hepatitis C, HBsAg and HIV virus antigen were negative.` rK39 dipstick test was negative.

Contrast Enhanced Computed Tomography(CECT) of abdomen revealed massive splenomegaly with a size of 24.5 cm in craniocaudal extent and a sub centimetric nodule noted in the lateral segment of middle lobe and laterobasal segment of right lower lobe. Subsequently bronchoalveolar lavage (BAL) was performed, which came negative on Cartridge Based Nucleic Acid Amplification Test(CBNAAT), cytology showed no atypical cells/granuloma and culture came positive for *S. Pneumonia* and *Klebsiella*.

He was managed as case of SMZL and chemotherapy by Rituximab and Bendamustine instituted as per standard protocol. As bone marrow was involved and a morphology along with Flow cytometry based diagnosis could be made, splenectomy was not performed in our patient.

Discussion

Splenic marginal zone lymphoma (SMZL) is a rare indolent Non-Hodgkin lymphoma (NHL) subtype accounting for <2 % of cases of lymphoid neoplasms which has an origin from the B memory lymphocytes present in the marginal zone of secondary lymphoid follicles [1]. It accounts for most cases of otherwise unclassifiable chronic lymphoid leukemias that are CD5 negative. Most patient are aged >50 years, with a median age of 67-68 years with equal predisposition to male and female [2]. SMZL affects the spleen, splenic hilar lymph nodes, bone marrow and peripheral blood. Patients with SMZL presents with symptomatic splenomegaly and cytopenia in the latter course of the disease [3]. Approximately 20% of patients have autoimmune manifestation including autoimmune hemolytic anemia, immune thrombocytopenia, cold agglutinin disease, circulating anticoagulants, acquired von Willebrand disease or angioedema [4]. Complete blood count often reveals absolute lymphocytosis in most of the cases. In peripheral blood cells, villous lymphocytes having round nuclei, condensed chromatin, basophilic cytoplasm with polar short villi are characteristic of SMZL and are required to differentiate SMZL from hairy cell leukemia.

Hairy process can be seen in other mature B-cell lymphoproliferative disorders and these include Splenic Diffuse Red Pulp Lymphoma (SDRPL) and Variant Hairy Cell Leukemia (HCL-v, now known as Splenic B cell lymphoma/leukemia with prominent nucleoli as per WHO 2022 guidelines [4]. Figure a shows the characteristic findings in peripheral blood, bone marrow and spleen along with immunophenotype, cytogenetic and molecular profile in various splenic lymphomas.

Character	SMZL	HCL	SDRPL	HCL-v
Peripheral blood morphology	Cells with scant cytoplasm, cleaved nucleus, small unevenly distributed villi / polar villi	Medium sized cells, abundant cytoplasm, numerous hair like villi, absent nucleoli Positive for TRAP (Special Stain)	Small cells with small, broad based villi, small distinct nucleoli	Intermediate size, Polar villi, prominent nucleoli
Bone marrow	Para-trabecular and sinusoidal	Interstitial to nodular/ diffuse fibrosis (Aspirate is often dry tap)	Sinusoidal +/− interstitial, rarely nodular	Interstitial and sinusoidal
Splenic involvement	White pulp	Red pulp with blood lakes	Red pulp with blood lakes	Red pulp with blood lakes
Immunophenotyping	CD5(-),CD10(-), CD20(+),CD79a(+) CD23(-), FMC7(+), CyclinD1(-), CD11c(+), CD103(+/-)	CD20(+), CD22(+), CD11c(+), annexin A1(+), CD103(+), CD25(+), CD5(-), CD10(+/-), FMC7(+), CD200(+)	CD20(+), CD72(+), IgG(+),IgD(-), CD5(-), annexin A1(-),CD10(-), CD25(-), CD23(-), CD103(+/-)	CD20(+), CD22(+), CD11c(+) , CD72(+) annexin A1(-), CD103(+), CD123(-) CD5(-), CD10(+/-), FMC7(+), CD200(-)
Molecular profile and Cytogenetics	Heterozygous 7q deletion, Trisomy of chromosome 3, Mutations of NOTCH2, KLF2	BRAF V600E mutation, IGHV4-34 mutation (in few BRAF V600E negative cases)	Mutations of CCND3, NOTCH1, MAP2K1	Deletion of 17p, 7q Mutations of TP53, MAP2K1

Figure a: Characteristic findings in peripheral blood, bone marrow and spleen along with immunophenotype, cytogenetic and molecular profile in various splenic lymphomas.

In the bone marrow, SMZL infiltration is classically nodular or intrasinusoidal. Immunohistochemistry shows a mature B phenotype with the expression of CD20 and CD79, without Cyclin D1, CD10, CD5, CD23 or BCL6 [5]. On flow cytometry, these cells are CD24+, CD27+, and FMC7+. They are classically stained by CD22 and CD11c but less bright than other splenic lymphomas (SDRPL or HCL). The CD123 is negative, and CD103 may be dim positive in rare cases. With both techniques, cases are usually negative for Annexin A1 and CD25. The addition of CD180 in the flow cytometry and immunohistochemistry panel has made it possible to better classify these lymphomas with sensitivity and specificity being 75% and 90%, respectively making CD180 a helpful immunologic marker in SMZL [6]. In our case, the pre-operative differential diagnoses were narrowed down to either lymphoplasmacytic lymphoma or SMZL, based on bone marrow studies and flow cytometry.

Though splenectomy was not performed in our patient, as we had a diagnosis based on peripheral smear, bone marrow aspirate and flow cytometry. However in few cases histopathological examination of the spleen is required for a confirmatory diagnosis of SMZL [7]. The spleen usually has a gross weight of more than 400 g (and may exceed 2000 g) and the cut surface shows a typical multi-micronodular pattern. SMZL develops in the white pulp with a biphasic picture. Medium-size monocytoid B cells are organized into a pale ring around the follicle with a MZ pattern, whereas small centrocyte-like cells efface the mantle zone and colonize the germinal centers. A variable degree of plasmacytic differentiation may be present. Lymphoma cells may involve the red pulp in patchy or diffuse fashion, with subsequent spread to the sinuses. Immunoblastic cytology suggests transformation into a more aggressive lymphoma [8]. Hilar lymph nodes, if involved, display a nodular proliferation with obliteration of the reactive germinal centers and engulfment of the sinuses [9]. However, Splenectomy is nowadays much less performed as a part of the treatment of SMZL, because there are alternatives, for both diagnosis and treatment as with the index case. It can now be established that, thanks to the cytological analysis and flow cytometry of peripheral blood or bone marrow aspirate which provide a faster and reliable diagnosis, post splenectomy histopathological diagnosis is not warranted [10]. Since patients with SMZL have been known to maintain remission for years after splenectomy alone, splenectomy is chosen for both diagnosis and treatment depending on the clinical background.

The first description of SMZL by Schmid., *et al*. relied on the recognition of a histologic pattern recapitulating the marginal zone (MZ), as observed in the splenic white pulp [11]. The most frequent cytogenetic abnormalities are 7q deletions (30-40%), likely in the loci 7q32 to 7q35, or trisomies of chromosomes 3 or 12, and even 1q, 8q, 18, or 6q deletions [12]. The 7q deletion is seen much more frequently in SMZL than similar B-cell neoplasms, and thus, it has even been proposed as a primary diagnostic marker. It is suggested that it may be a causative event rather than a simple pro-survival signal. The molecular pathway involves NOTCH receptor genes which encodes a heterodimeric transmembrane proteins functioning as ligand-activated transcription factors [13]. These on activation recruits the MAML1 and MAML2 transcriptional cofactors to modify the expression of several target genes. Genes of the NOTCH pathway is mutated in ~40% of SMZLs. NOTCH2 shows recurrent mutations in ~10% to 25% of SMZLs, establishing NOTCH2 as one of the most frequently mutated genes in this lymphoma. NOTCH1, a paralog of NOTCH2, is also mutated in an additional ~5% of SMZL [12,14].

According to Lugano classification, SMZL is not fluorodeoxyglucose-avid disease and must be staged by means of computed tomography [15]. A complete response (CR) is achieved when splenomegaly has been resolved, blood cell counts are normalized, flow cytometry on blood is negative, and BM histology is negative by immunohistochemistry. As a surgical approach, Laparoscopic surgery is preferred as decreased blood loss and fewer complications, compared with those of open splenectomy. According to the European Society for Medical Oncology guidelines, rituximab monotherapy is a reasonable first-line therapy and a less traumatic alternative to splenectomy [16]. Hepatitis C virus infection has been reported to be related with the etiology of SMZL, thereby prompting ways for the novel treatment options that include antiviral agents. The causal role of Hepatitis C Virus (HCV) in SMZL is strongly supported by the regression of lymphoma after eradicating the HCV infection [17]. Purine analogs are more toxic and are reserved for refractory or relapsed cases. Fludarabine has high response rates, with complete remission in 70% of cases and progression-free survival of 4.7 years. The summary of how to approach a case of SMZL based on our experience and reviewing the existing literature is given below in Figure 5.

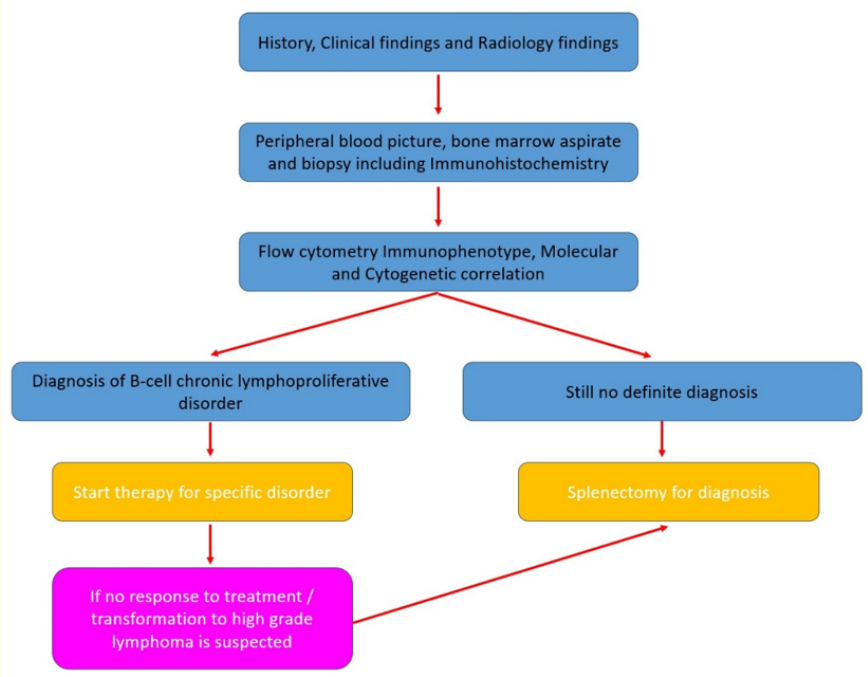

Figure 5: How to approach a case of SMZL.

Conclusion

SMZL presents many unsolved questions, such as standard prognostic criteria and best treatment protocols because the clinical, immunophenotypic and genetic features of SMZL are different from other marginal zone lymphomas. As it comprises only less than 2% of lymphomas and large randomized clinical trials are not possible, case reports and series are important for future prospective analyses to find powerful prognostic criteria including clinical, immunophenotypic and cytogenetic markers specifically associated with SMZL.

Bibliography

1. Arcaini L., *et al*. "Splenic marginal zone lymphoma: from genetics to management". *Blood* 127.17 (2016): 2072-2081.

2. Alaggio R., *et al*. "The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms". *Leukemia* 36.7 (2022): 1720-1748.

3. Koyama R., *et al*. "Splenic marginal zone lymphoma treated with laparoscopic splenectomy: A case report". *International Journal of Surgery Case Reports* 65 (2019): 288-291.

4. Yilmaz E., *et al*. "A Review on Splenic Diffuse Red Pulp Small B-Cell Lymphoma". *Current Oncology* 28.6 (2021): 5148-5154.

5. Cho J. "Basic immunohistochemistry for lymphoma diagnosis". *Blood Research* 57 (2022): 55-61.

6. Donzel M., *et al*. "New Insights into the Biology and Diagnosis of Splenic Marginal Zone Lymphomas". *Current Oncology* 28.5 (2021): 3430-3447.

7. Zhang S., *et al*. "Splenic marginal zone lymphoma: a case report and literature review". *World Journal of Surgical Oncology* 18.1 (2020): 259.

8. Conconi A., *et al*. "Histologic transformation in marginal zone lymphomas†". *Annals of Oncology* 26.11 (2015): 2329-2335.

9. Mollejo M., *et al*. "Lymph node involvement by splenic marginal zone lymphoma: morphological and immunohistochemical features". *The American Journal of Surgical Pathology* 21.7 (1997): 772-780.

10. Sah SP., *et al*. "A comparison of flow cytometry, bone marrow biopsy, and bone marrow aspirates in the detection of lymphoid infiltration in B cell disorders". *Journal of Clinical Pathology* 56.2 (2003): 129-132.

11. Schmid C., *et al*. "Splenic marginal zone cell lymphoma". *The American Journal of Surgical Pathology* 16.5 (1992): 455-466.

12. Salido M., *et al*. "Cytogenetic aberrations and their prognostic value in a series of 330 splenic marginal zone B-cell lymphomas: a multicenter study of the Splenic B-Cell Lymphoma Group". *Blood* 116.9 (2010): 1479-1488.

13. Wang MM. "Notch signaling and Notch signaling modifiers". *The International Journal of Biochemistry and Cell Biology* 43.11 (2011): 1550-1562.

14. Rossi D., *et al*. "The coding genome of splenic marginal zone lymphoma: activation of NOTCH2 and other pathways regulating marginal zone development". *Journal of Experimental Medicine* 209.9 (2012): 1537-1551.

15. Cheson BD., *et al*. "Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification". *Journal of Clinical Oncology* 32.27 (2011): 3059-3068.

16. Olszewski AJ and Ali S. "Comparative outcomes of rituximab-based systemic therapy and splenectomy in splenic marginal zone lymphoma". *Annals of Hematology* 93.3 (201): 449-458.

17. Iannitto E and Tripodo C. "How I diagnose and treat splenic lymphomas". *Blood* 117.9 (2011): 2585-2595.