Case Report

Unexpected Presentation for Predicted Complication Orbital Lymphoma in a patient with Primary Sjögren Syndrome

Mustafa E. Omran[1], Asaad A. Khalaf[2], Raghda I. Saleem[3]

1. Lecturer, Department of Medicine, Al-Zahraa College of Medicine, University of Basrah, Basrah, Iraq
2. Haematology Subspecialty senior, Head of Haematology Department, Al-Sayyab Teaching Hospital, Basrah, Iraq
3. Assistant lecturer, Department of Family and Community medicine , College of Medicine, University of Basrah, Basrah, Iraq.

Received: 10.12.2023 Accepted: 23.12.2023

Abstract

Lymphoid malignancies are the most common primary orbital tumours but they constitute only 2% of extranodal lymphomas. A fifty-year-old lady known case of SS presented with progressive blurred vision and left deep orbital pain for about 5 months duration, with time, she started to develop left eye protrusion with ophthalmoplegia. The histopathological diagnosis was a low-grade follicular (nodular) B cell subtype of non-Hodgkin lymphoma (Grade 2). Immunohistochemically, it displayed CD45 and CD20 positive, stained whole neoplastic variables sizes follicles, CD3 stained rime of non-neoplastic T cells around the follicles. Positron Emission Scan (PET scan) exhibited mild hyper-metabolic multiple right cervical and supraclavicular lymph nodes and moderately hypermetabolic enlarged abdominal lymph nodes. The patient after the 4th cycle of chemotherapy has no palpable cervical lymphadenopathy and restores the normal vision in the left eye.

Keywords: Sjogren syndrome, orbital lymphoma, Basrah

Corresponding author: **Raghda I. Saleem,** Department of Family and Community Medicine, College of Medicine, University of Basrah, Basrah, Iraq.

✉ **E-mail:** raghdaalbaldawi@gmail.com

Introduction

Sjögren Syndrome is distinct among autoimmune diseases as for malignant conversion hazard; those patients appear to have a 10-44-fold greater risk of developing lymphoma compared to the general population (Seven-fold and four-fold greater risk for Systemic Lupus Erythematosus and Rheumatoid Arthritis respectively.[1,2,3] A 2.7–9.8% of Sjögren Syndrome patients are recognized with Non-Hodgins Lymphoma (NHL) and that risk increases by 2.2% per year of age.[4] Mucosa-associated lymphoid tissue (MALT) lymphomas signify 60% of cases. The commonest locations are the salivary glands, particularly the parotid and submandibular glands, but the orbits, nasopharynx, stomach, thyroid, and lung may be involved.[5] Additional subtypes of lymphoma that can originate in these patients are the diffuse large B-cell lymphoma (DLBCL) and the nodal marginal zone lymphoma (NMZL), which constitute with MALT more than 90% of total SS-associated lymphoma cases, in Sjögren Syndrome patients with both MZL and DLBCL these tumors are usually clonally related, which most likely shows that high-grade DLBCL developed from low-grade MZL.[1,2] The cause of

molecular derivation of malignant transformation is still largely vague and undefined.[6] Current beliefs about lymphomatous changes emphasise four interconnected characteristics: chronic Inflammation, B-cell Activation, defective Immunosurveillance, and epigenetic Alterations.[7] A focus score of at least 3 in Minor Salivary Gland Biopsies of SS patients has been documented as an independent and important expectant influence for NHL development (Positive predictive value of (16%), Negative predictive value of (98%).[8] The inflammasomes activation model secondary to accumulation and buildup of proinflammatory nucleic acid debris That are in completely degraded and removed, has recently been reinforced.[9,10] On the other hand, stimulation of chronic inflammation appears to be linked to IFN-γ, as the mRNA levels in MSGBs have been associated with a higher degree of lymphocytic recruitment and infiltration, shown to be an inducing factor for lymphomagenesis. IFNγ /IFNα mRNA ratio in MSGBs has emerged as a histopathological biomarker for the expectation of future in situ lymphoma progress.[11] B-cell activating factor (BAFF) is regulated by both type I and II IFNs manufactured by numerous immune cells and also by salivary glands epithelial cells.[12] BAFF is fundamental for the maturation of B cells, proliferation of B cells, and Survival of B cells. It is found that BAFF levels are amplified in SS patients' serum with a history of lymphoma and continue to be in high levels for years after treatment and even after remission.[13-15] The chain of events encompassing autoreactive B-cell chronic stimulation and immune complexes formation might lastly lead to the critical, monoclonal expansion of rheumatoid factor (RF)-reactive B cells and the lymphomatous transformation, malfunctioning immune-surveillance.[12] Over-expression of Bcl-2 due to a translocation including chromosomes 14 and 18, leading to inhibition of apoptosis and increased B-cell survival. Apart from the IFNα effect on p53 levels, the precise mutations of this tumor suppressor gene were described 20 years ago in Minor salivary gland biopsies from patients with Sjögren Syndrome associated Non-Hodgkin's Lymphoma cases.[15,16]

Case

Fifty year-old lady presented with progressive blurred vision and left deep orbital pain for about 5 months duration, with time, she started to develop left eye protrusion with ophthalmoplegia. She also suffered from mild fatigue, 2 Kg Weight Loss, occasional low-grade fever, and rarely tension-type headache. She was diagnosed with Sjögren Syndrome in 2012 with frequent consultations in Baghdad Medical City Complex and medical private clinics in Baghdad and Basrah and she received multiple medications including MTX, HCQ and Steroids (Oral and Parenteral). She previously had thyromegaly for which she underwent thyroidectomy in Basrah General Hospital in 2014 for unknown reasons. Reviewing her investigations revealed that anti-Ro antibodies were positive repeatedly but anti-La and Thyroid Peroxidase (TPO) antibodies, were negative. ANA is weakly positive (low titer). Anti (dsDNA) negative, (RF) and (ACCP) antibodies were negative time after time. Serial inflammatory markers all were normal apart from progressive increment. On Examination she was vitally stable, with exophthalmos and ophthalmoplegia of the left eye, cervical lymphadenopathy was observed and palpated, and clear scars from previous thyroidectomy & LN Biopsy. Normal lower limbs examination (No Rash or Purpura), the abdomen was soft with no splenomegaly, cardiac auscultation was

normal, and chest auscultation was normal with equal air entry. Blood investigations were normal (Complete blood picture with white blood cell Counts (8.3×10^9) with normal cell differentials, Hb (11.7) g/dl, MCV (93) FL, Platelet count was (268×10^9), ESR (30,45) then 52 mm/2hr, Creatinine (0.8) mg/dL, Complement levels (C3 & C4) were normal). She was on a Thyroxine tablet 100 mcg once daily for iatrogenic hypothyroidism, an Amlodipine tablet 5mg with a Valsartan tablet 160 mg both once daily for her blood pressure control and recently, Artificial tears with Hydroxychloroquine tablet 200 mg were added in addition to Methylprednisolone tablet (Medrol) 4 mg.

MRI of the head was performed and revealed non-homogenous enhancement and infiltration of the left lateral rectus muscle (Thickening of the muscle belly and tendinous insertion) with diffuse enlargement of the left lacrimal glands. (Shown in the figure-1)

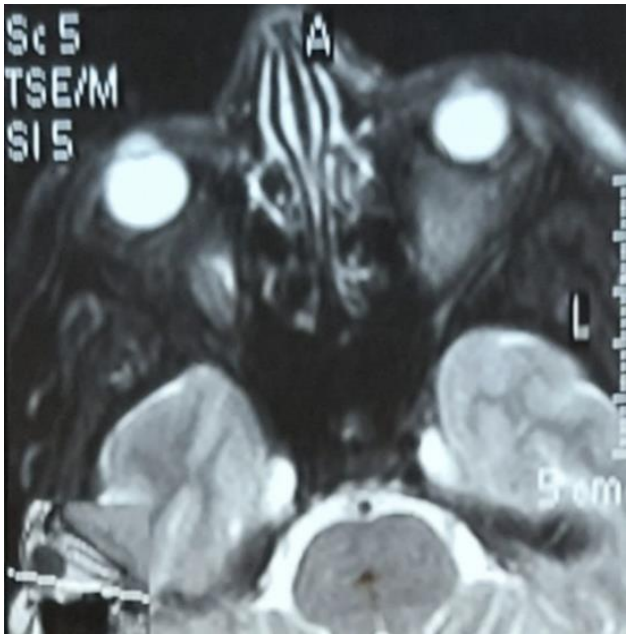

Fig 1. Orbital MRI shows enhanced lateral rectus muscleewith diffuse lacrmial gland enlagments

The gross appearance of cervical lymph node biopsy revealed a single lymph node measuring 2.8 cm with an intact fibrous capsule, and a fleshy homogenous cut section, The histopathological diagnosis was low-grade follicular (nodular) B cell subtype of Non-Hodgkin Lymphoma (Grade 2). Immunohistochemically, it displayed CD45 and CD20 positive, stained whole neoplastic variables sizes follicles, CD3 stained rime of Non-neoplastic T cells around the follicles.

Another review of the slides of lymph node biopsy by Baghdad Teaching Hospital (Histopathology Department) revealed partial effacement of nodal architecture by a perifollicular expansion of small lymphoid cells with clear cytoplasm, The neoplastic cells were positive for CD 20, Pax 5, and bcl 2 and negative for CD5, CD10, CD23, bcl 16, cyclin D1, Features compatible with low-grade marginal zone NHL.

Positron Emission Scan (PET scan) exhibited mild hyper-metabolic multiple right cervical and supraclavicular lymph nodes. Moderately hypermetabolic enlarged abdominal (Left Para-aortic, bilateral common iliac, right external and inguinal lymph nodes) but no evidence of hypermetabolic mediastinal, hilar or axillary lymph nodes. (Figure 2)

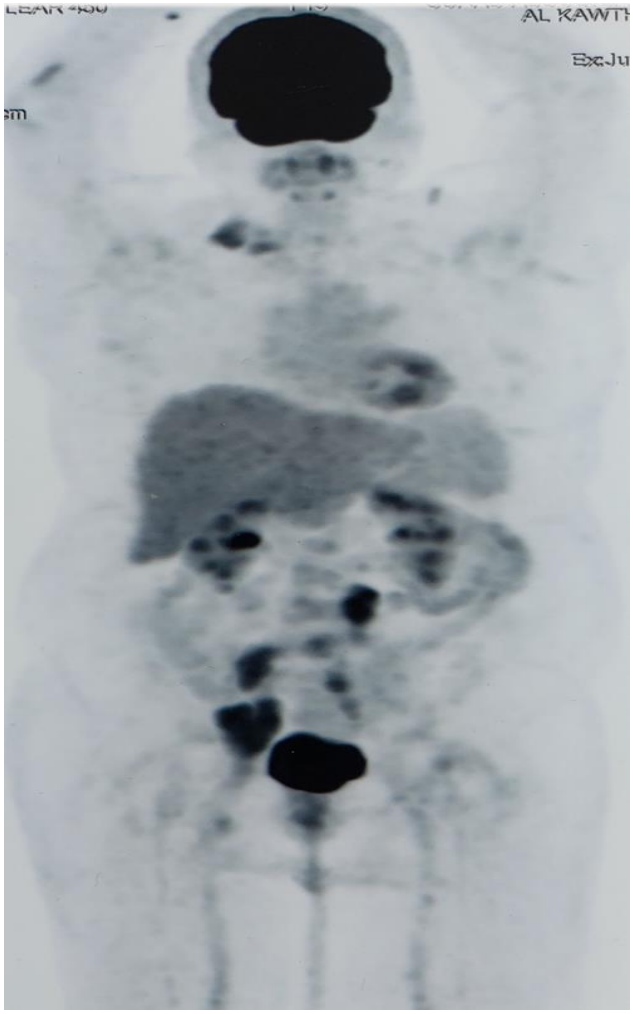

Fig 2. PET scan demonstrated mild hypermetabolic multiple right cervical and supraclavicular lymph nodes with Moderately hypermetabolic enlarged abdominal lymphnodes.

She was treated with four cycles of Bendamustine (Bendeka®) with Rituximab (R-Benda), the goal of such therapy is to shrink lymph nodes and decrease symptoms but not for the intention of cure. Such a regime may induce and maintain remission for months to even years which is an attractive short-term target. The treatment was scheduled as follows:

1. Rituximab intravenous infusion on Day 1
2. Bendamustine I.V. infusion over sixty minutes on Days 1 and 2

Bendamustine and Rituximab were given to the patients in a Hemato-Oncology outpatient clinic and the cycle was repeated every 4 weeks for 4 cycles. In General, the number of given cycles depends upon the stage of the disease. Duration of therapy may last up to six months, depending upon response and tolerance.The patient after the 4th cycle of chemotherapy has no palpable cervical lymphadenopathy and restores normal vision in the left eye. The New PET Scan shows a complete metabolic response without any disease residue. Moreover, her European Sjögren Syndrome Disease Activity Index (ESSDAI) score declines from19 to 12

Discussion

Lymphoid malignancies are the most common primary orbital tumours but they constitute only 2% of extranodal lymphomas.[17] The occurrence of lymphoma in patients with primary Sjögren syndrome is well-known and expected long-term complication for excessive and uncontrolled autoimmune activity. The current patient has had only marginal sicca symptoms and ceases follow-up because of the recognized chronicity of the disorder and the absence of well-organized immune-modulating therapy that can mitigate Primary Sjögren syndrome the symptoms of dryness and the other systemic symptoms of Sjögren Syndrome. The fundamental note here is to enforce the patient with Primary Sjögren syndrome to keep on follow-up and be aware the physician in charge imposes a high degree of suspicion about such complications that still have had depressing prognosis, and upon diagnosis, an extensive workup should be carried out to stage this malignancy and figure out any associated disease and comorbidities to facilitate patient categorization. Even though there are no cures for such dismal complications, it is worth bringing

the disease under control and improving the quality of life with widely available less toxic conventional and biological (Monoclonal antibody) medications, especially with the support of expert hemato-oncologists seniors. Monoclonal antibody therapy may not only be as effective as other therapies for local control of orbital and ocular adnexal lymphoma but also may suggest superior overall systemic control of lymphoma.[18] Watch-and-wait strategy is recommended as an acceptable treatment option for patients with advanced-stage, low-grade B-cell lymphoma, especially for those with follicular lymphomas which is not the case in our patient, Though, the validity of the watch-and-wait strategy is yet still debatable because it has not been evaluated in large number of patients with MALT lymphoma.[19] Although the presentation of this patient was relatively unexpected, on occasion the presentation of ocular marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue could be quite unusual, an example camouflaged case as Chalazion reported by Syafiq. Etal.[20] Symptoms are highly unspecific and essentially result from mass effect as our patient, but rapid expansion may suggest the malignant nature of the disease.[21] Individually, the studied case is considered a disseminated disease, so the best option to control the symptoms and reduce the tumour bulk will be anti-CD 20 (Rituximab) based chemotherapy which was proven previously in many studies and was used with our case successfully. [22]

References

1. Brito-Zerón P, Kostov B, Fraile G, Caravia-Durán D, Maure B, Rascón F-J, et al. Characterization and risk estimate of cancer in patients with primary Sjögren syndrome. J Hematol Oncol [Internet]. 2017; 10(1):90.
2. Meijer JM, Meiners PM, Vissink A, Spijkervet FKL, Abdulahad W, Kamminga N, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double blind, placebo-controlled trial. Arthritis Rheum. 2010; 62(4): 960-968.
3. Alunno A, Leone MC, Giacomelli R, Gerli R, Carubbi F. Lymphoma and lymphomagenesis in primary Sjögren's syndrome. Front Med [Internet] 2018; 5(April):102
4. Chiu YH, Chung CH, Lin KT, Lin CS, Chen JH, Chen HC, Huang RY, Wu CT, Liu FC, Chien WC. Predictable biomarkers of developing lymphoma in patients with Sjögren syndrome: a nationwide population-based cohort study. Oncotarget. 2017 Jul 25; 8(30):50098-50108
5. Brito-Zerón P, Kostov B, Fraile G, Caravia-Durán D, Maure B, Rascón F-J, et al. Characterization and risk estimate of cancer in patients with primary Sjögren syndrome. J Hematol Oncol. 2017; 10(1):90.
6. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. Nat Rev Rheumatology. 2018; 14(3):133-145.
7. Nocturne G, Mariette X. Sjögren syndrome-associated lymphomas: an update on pathogenesis and management. Br J Haematol. 2015;168(3): 317-327.
8. Risselada AP, Kruize AA, Goldschmeding R, Lafeber FPJG, Bijlsma JWJ, Van Roon JAG. The prognostic value of routinely performed minor salivary gland assessments in primary Sjögren's syndrome. Ann Rheum Dis. 2014;73(8):1537-1540.
9. Baldini C, Santini E, Rossi C, Donati V, Solini A. The P2X7 receptor-NLRP3 inflammasome complex predicts the

development of non-Hodgkin's lymphoma in Sjögren's syndrome: a prospective, observational, single-centre study. J Intern Med. 2017; 282(2):175-186.

10. Vakrakou AG, Boiu S, Ziakas PD, Xingi E, Boleti H, Manoussakis MN. Systemic activation of NLRP3 inflammasome in patients with severe primary Sjögren's syndrome fueled by inflammagenic DNA accumulations. J Autoimmun [Internet]. 2018 [cited 2018 Sep 30]; 91:23-33
11. Hall JC, Baer AN, Shah AA, Criswell LA, Shiboski CH, Rosen A, et al. Molecular subsetting of interferon pathways in Sjögren's syndrome. Arthritis Rheumatol. 2015; 67(9):2437-2446.
12. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. Nat Rev Rheumatol. 2018;14(3):133-145.
13. Quartuccio L, Salvin S, Fabris M, Maset M, Pontarini E, Isola M, et al. Blys upregulation in Sjögren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B-cell clonal expansion in the salivary glands. Rheumatology (United Kingdom). 2013; 52(2):276-281.
14. Nezos A, Gravani F, Tassidou A, Kapsogeorgou EK, Voulgarelis M, Koutsilieris M, et al. Type I and II interferon signatures in Sjögren's syndrome pathogenesis: contributions in distinct clinical phenotypes and Sjogren's related lymphomagenesis. J Autoimmun [Internet]. 2015; 63:47-58.
15. Nezos A, Papageorgiou A, Fragoulis G. et al. B-cell activating factor genetic variants in lymphomagenesis associated with primary Sjögren's syndrome. J Autoimmun [Internet]. 2014; 51:89-98.
16. Tapinos NI, Polihronis M, Moutsopoulos HM, et al. Lymphoma development in Sjögren's syndrome: novel p53 mutations. Arthritis Rheum. 1999; 42(7):1466-1472.
17. Esmaeli B, Murray L, Ahmadi MA. et al. Immune therapy for low grade Non-Hodgkin's secondary Lymphoma of the orbit, Arch Ophalmol/ Vol 120 Sep 2002; 1225-1227
18. Hatef E, Roberts D, McLaughlin P.et al. Prevalence and Nature of Systemic Involvement and Stage at Initial Examination in Patients With Orbital and Ocular Adnexal Lymphoma. Arch Ophthalmol /Vol 125 (No. 12), Dec 2007
19. Tanimoto K, Kaneko A, Suzuki S. Long-term follow-up results of no initial therapy for ocular adnexal MALT lymphoma. Annals of Oncology17: 2006; 135-140
20. Syafiq NA, Azida JW, Reddy SC. et al, Ocular marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue masquerading as chalazion: a case report. Malaysian Journal of Ophthalmology 2021; 1:57-63
21. Sandner A, Surov B, Bach AG. et al. Primary extranodal Non-Hodgkin lymphoma of the orbital and paranasal region-A retrospective study. European Journal of Radiology 82 (2013) 302-308.
22. Hindso TG, Esmaeli B, Holm F.et al. International multicenter retrospective cohort study of ocular adnexal marginal zone B-cell lymphoma. Br J Ophthalmol 2019; 0:1-6.

عرض غير متوقع للمضاعفات المتوقعة سرطان الغدد الليمفاوية المدارية في مريض مصاب بمتلازمة (Sjögren) الأولية

الأورام اللمفاوية الخبيثة هي الأورام المدارية الأولية الأكثر شيوعا ولكنها تشكل ٢٪ فقط من الأورام اللمفاوية الخارجية. قدمت سيدة تبلغ من العمر خمسين عاما حالة معروفة من SS مع عدم وضوح الرؤية التدريجي وترك الألم المداري العميق لمدة ٥ أشهر تقريبا، مع مرور الوقت، بدأت في تطوير نتوء العين اليسرى مع شلل العين. كان التشخيص النسيجي المرضي نوعا فرعيا من الخلايا البائية الجريبية منخفضة الدرجة (عقيدية) من سرطان الغدد الليمفاوية اللاهودجكين (الدرجة ٢). من الناحية المناعية الكيميائية، عرضت CD45 و CD20 إيجابية، وأحجام متغيرات الأورام الكاملة الملطخة، وحافة ملطخة CD3 للخلايا التائية غير الورمية حول البصيلات. أظهر فحص الانبعاث البوزيتروني (PET scan) الغدد الليمفاوية العنقية وفوق الترقوة المفرطة الأيض والغدد الليمفاوية البطنية المتضخمة بشكل معتدل. المريض بعد دورة ٤ من العلاج الكيميائي ليس لديه اعتلال العقد اللمفية عنق الرحم واضح ويعيد الرؤية الطبيعية في العين اليسرى.