CASE REPORT

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Thymic mucosa-associated lymphoid tissue lymphoma in a patient with Sjögren's syndrome with cutaneous vasculitis

Limfom ekstranodusnog limfnog tkiva u sastavu sluznica u timusu bolesnika sa Sjegrenovim sindromom i vaskulitisom kože

Ksenija Božić*†, Dragan Živojinović‡, Ljubinko Djenić§, Lavinika Atanasković*‖

***University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; Military Medical Academy, †Clinic for Rheumatology, ‡Institute of Pathology, §Clinic for Thoracic Surgery, ‖Clinic for Hematology, Belgrade, Serbia**

Abstract

Introduction. The association between Sjögren's syndrome (SS) and the development of lymphoma is well known. The prevalence of lymphoma in patients with SS is 5%. Mucosa-associated lymphoid tissue (MALT) lymphoma is the most common lymphoma type in patients with SS. It is common for MALT lymphoma to develop in the stomach, while it is extremely rare in the thymus. **Case report.** We present a 61-year-old Caucasian male patient with primary SS, cutaneous vasculitis, and thymic MALT lymphoma. The patient had a two-year history of diffuse cutaneous palpable purpura on legs, intermittently enlarged left parotid gland, and dry mouth. The results of Schirmer's test were positive, labial salivary glands biopsy revealed a focus score ≥ 1, serology testing showed positive anti-Ro/SS-A and anti-La/SS-B antibodies, while skin biopsy findings revealed leukocytoclastic vasculitis. Diagnosis of primary SS with extraglandular cutaneous manifestations was confirmed. Cryoglobulinemia (Cg) and monoclonal gammopathy (MG) were detected, which increased the suspicion of hematological malignancy, and additional diagnostic procedures were performed. Computed tomography of the chest revealed an enlarged, multicystically altered anterior mediastinal mass. A thymectomy was performed through video-assisted thoracic surgery. Histological findings of the tissue confirmed the presence of tumor tissue consistent with MALT lymphoma in the thymus. Induction therapy with pulse doses of glucocorticoids was applied for three days, which was continued with medium doses of the drug. The doses were gradually reduced, and hydroxychloroquine was introduced. This has shown to be an effective therapy against features of SS. Postoperative local radiotherapy was performed. **Conclusion.** In SS patients with CV and in the presence of Cg and MG, attention should also be paid to the eventual development of MALT lymphoma, including the rare localization in the thymus.

Key words:
cryoglobulinemia; lymphoma, b-cell, marginal zone; sjogren's syndrome; thymus neoplasms; vasculitis, leucocytoclastic, cutaneous.

Apstrakt

Uvod. Veza između Sjegrenovog sindroma (SS) i nastanka limfoma je dobro poznata. Prevalencija limfoma kod bolesnika sa SS je 5%. Limfom ekstranodusnog limfnog tkiva u sastavu sluznica (*mucosa-associated lymphoid tissue* - MALT) je najčešći tip limfoma kod bolesnika sa SS. MALT limfom se često razvije u želucu dok je u timusu veoma redak. **Prikaz bolesnika.** Prikazujemo bolesnika starog 61 godinu, bele rase, sa primarnim SS i vaskulitisom kože (VK) i MALT limfomom u timusu. Bolesnik je imao difuznu palpabilnu purpuru na koži nogu prethodne dve godine, intermitentno uvećanje leve parotidne žlezde i osećaj suvih usta. Rezultati Širmerovog testa bili su pozitivni, histopatološki nalaz biopsije labijalnih pljuvačnih žlezda pokazao je fokus skor ≥ 1, serološkim analizama pokazana je pozitivnost na autoantitela anti-Ro/SS-A i anti-La/SS-B, a histopatološki nalaz biopsije kože potvdio je leukocitoklastični vaskulitis. Dijagnoza SS sa vanžlezdanom kutanom manifestacijom bila je potvrđena. Detektovane su krioglobulinemija (Kg) i monoklonska gamopatija (MG), što je povećalo sumnju na postojanje hematološke maligne bolesti i sprovedene su dodatne dijagnostičke procedure. Kompjuterizovanom tomografijom grudnog koša utvrđena je uvećana, multicistično izmenjena masa u prednjem medijastinumu. Urađena je timektomija primenom video-asistirane torakalne hiruške intervencije. Histopatološkim nalazom tkiva potvrđeno je prisustvo tumorskog tkiva koje je po karakteristikama odgovaralo MALT limfomu u timusu.

Correspondence to: Ksenija Božić, Military Medical Academy, Clinic for Rheumatology, Crnotravska 17, 11 000 Belgrade, Serbia.
E-mail: kseksi@yahoo.com

Primenjena je indukciona terapija pulsnim dozama glukokortikoida tokom tri dana koja je nastavljena srednjim dozama leka. Doze su postepeno smanjivane i uveden je hidroksihlorokin. Ova terapija se pokazala kao delotvorna protiv manifestacija SS. Postoperativno je sprovedena lokalna radioterapija. **Zaključak.** Kod bolesnika sa SS i VK, i sa prisustvom Kg i MG, neophodno je obratiti pažnju na eventualni razvoj MALT limfoma, uključujući i veoma retku lokalizaciju u timusu.

Ključne reči:
krioglobulinemija; limfom, b-ćelijski, marginalna zona; sjegrenov sindrom; timus, neoplazme; koža, vaskulitis, leukocitoklastični.

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma is an extranodal variant of marginal zone B-cell lymphoma, a distinct subtype of non-Hodgkin lymphoma (NHL). It is characterized by an indolent clinical course and typical histopathological features. It accounts for 7–8% of all B-cell lymphomas and usually occurs in the gastrointestinal tract in up to 50% of all cases. Other sites include the lungs, salivary glands (SG), ocular adnexa, skin, thyroid gland, breasts, and liver, whereas MALT in the thymus is very rare [1]. More than 40 years ago, Isaacson [2] defined the thymic MALT lymphoma (TML). Among patients with TML, approximately 80% of cases were Asian, the female-to-male ratio was 3 : 1, and the presence of cysts was often detected radiographically [3]. MALT lymphoma is frequently linked to chronic immune stimulation by bacterial or viral agents and autoimmune diseases, especially Sjögren's syndrome (SS), as well as with Hashimoto thyroiditis [4, 5]. We presented a rare case of a Caucasian male patient with primary SS, cutaneous vasculitis (CV), and TML.

Case report

A 61-year-old Caucasian man was admitted to our hospital for high suspicion of SS and CV. During the last two years, the patient suffered from recidivans diffuse purpura on the legs, myalgia of the legs, and painful knees. He had acute parotitis two times in the last six months. Furthermore, he had a dry mouth but not dry eyes. He complained of severe fatigue. Physical examination revealed an enlarged left parotid gland and cutaneous diffuse palpable purpura on the lower extremities. Blood tests showed: erythrocyte sedimentation rate 108 mm/h [reference range (RR) < 20 mm/h], C-reactive protein level 8.11 mg/L (RR 0–5 mg/L), leukocyte count 5.41 × 10^9/L (RR 4–11 × 10^9/L), lymphocyte count 1.01 × 10^9/L (RR 0.9–5.2 × 10^9/L), erythrocyte count 3.70 × 10^{12}/L (RR 3.8–5.8 × 10^{12}/L), hemoglobin level 110 g/L (RR 130–180 g/L), platelet count 259 × 10^9/L (RR 160–370 × 10^9/L). Results showed elevated serum IgA level [7.17 g/L, normal range (NR) < 3.5 g/L]. Serum monoclonal gammopathy (MG) was detected. Rheumatoid factor level was elevated (121 IU/mL, NR < 15 IU/mL), antinuclear antibodies were positive with a titer of 1/160, speckled pattern, anti-Ro/SS-A antibody was 220 IU/mL (NR 0–20 IU/mL) and anti- La/SS-B antibody was 60 IU/mL (NR 0–20 IU/mL), while the remaining antibodies to extractable nuclear antigens and anti-double stranded DNA were negative. Cryoglobulins were slightly positive. Extensive infectious disease workup, including hepatitis B, hepatitis C virus (HCV), Epstein-Barr virus, cytomegalovirus, parvovirus, herpes simplex, and human immunodeficiency virus, was negative. Labial salivary gland biopsy revealed lymphocytic infiltration focus (≥ 1) without neoplastic cells (Figure 1). The patients fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SS [6]. Histological findings of skin biopsy revealed leukocytoclastic vasculitis. According to the above, the EULAR SS Disease Activity Index (ESSDAI) at SS diagnosis was 12. The patient was treated with pulse doses of methylprednisolone 500 mg daily for three days, followed by a dose of 0.5 mg/kg, with gradual dose tapering. Hydroxychloroquine was introduced at 400 mg daily. Smoking habit, the presence of cryoglobulinemia (Cg), MG, as well as CV increased suspicion of hematological malignancy and led to further diagnostic procedures – computed tomography (CT) of the whole body and bone marrow biopsy. CT of the chest revealed a retrosternal anterior mediastinal mass in the thymic region, dimensions 80 × 42 × 30 mm, with a multicystic appearance with part of fibrous changes (Figure 2). The video-assisted thoracic surgery (VATS) thymectomy was performed. Histological findings of the resected thymus tissue presented a lymphoma with heterogeneous diffuse infiltration of lymphocytes, centrocyte-like cells, monocyte-like cells, plasma, and blastoid cells (Figure 3A). Immunohistochemistry revealed positivity for CD20, CD79a, PAX5, and Bcl-2 in the neoplastic cells, while Bcl-6, CD10, cyclin D1, CD3, CD5, CD23, TdT, and CD1 were negative (Figure 3B). A low proliferative Ki-67 index was observed in up to 15% of neoplastic cells. Moreover, residual CK7 positive epithelioid thymic cells were detected in tumor tissue (Figure 3C).

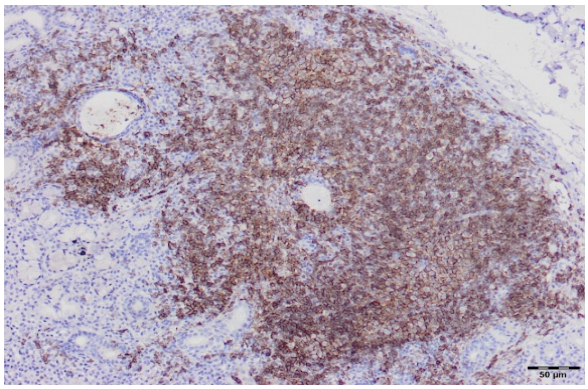


Fig. 1 – Histological findings of labial salivary glands biopsy. Immunohistochemical staining showing lobular infiltration with CD20 positive B-cells (HE, ×100).
HE – Hematoxylin and Eosin.

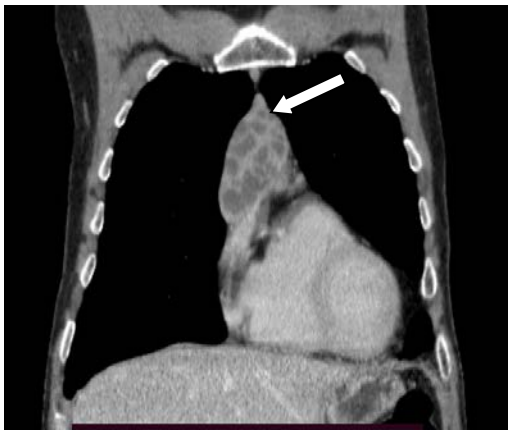
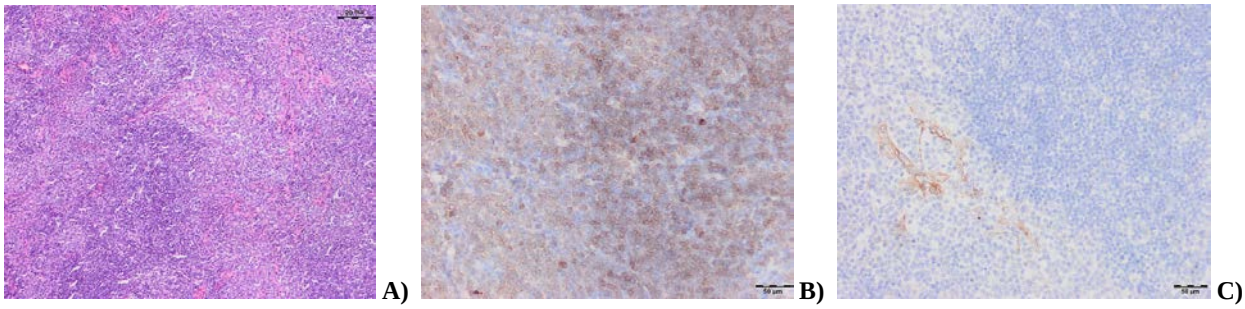


Fig. 2 – Computed tomography images reveal a large multicystic retrosternal mass in the anterior mediastinum (arrow).



A) B) C)

Fig. 3 – Histological findings of thymus tissue biopsy. Immunohistochemical staining showing: A) extranodal marginal zone B-cell lymphoma (HE, ×100); B) diffuse positivity for CD79a in neoplastic cells (HE, ×200); C) residual CK7 positive epithelioid cells (HE, ×200).
HE – Hematoxylin and Eosin.

Considering the results of all the tests that were done, a final diagnosis of extranodal non-Hodgkin lymphoma – MALT lymphoma in the thymus, was made. Bone marrow biopsy was without the presence of lymphoma. Post-tumor excision with the appliance of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}FDG-PET/CT) did not show probable postoperative residual lesions. Radiotherapy was performed with 24 Gy in eight courses. As an outpatient on follow-up after 20 months, the patient was without purpura, parotitis, or any systemic complaints. His therapy was prednisolone 5 mg every other day and 400 mg of hydroxychloroquine *per* day. Chest CT did not show any residue of tumor tissue.

Discussion

Primary SS is a systemic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands, mainly the lacrimal and SG, leading to reduced secretory capacity. A subgroup of patients has experienced extraglandular manifestations that can involve any organ or system and worsen the disease outcome [7]. In addition to systemic manifestations, such as interstitial lung disease and cryoglobulinemic vasculitis, lymphoma is a systemic complication that leads to premature mortality in SS, adding an excess death rate of 9.4 cases *per* 1,000 patient at risk *per* year [8]. Among patients with autoimmune diseases, patients with SS are at a higher risk of developing lymphoma compared to patients with other autoimmune diseases (4-fold or 7-fold to patients with rheumatoid arthritis or systemic lupus erythematosus, respectively) and at an even higher risk compared to the general population (> 10-fold) [9]. The pathogenic role of B-cells in SS is a main feature of the disease, including the presence of circulating autoantibodies, alterations in peripheral B-cell subpopulations, B-cell predominance in advanced SG lesions, and increased risk of developing NHL B-cell MALT lymphoma in SS [10]. Lymphomagenesis in SS arises from persistent polyclonal B-cell activation due to chronic antigen stimulation in the SG, which can lead to oligoclonal/monoclonal B-cell expansion followed by the selection of premalignant B-cell clones and progress to lymphoma [11, 12]. Many predictors of lymphoma in SS have been investigated in the last several years. The most clinically relevant lymphoma predictor is persistent salivary gland enlargement (SGE), and then Cg and CV [13]. Although SGE is present in about one-third of SS patients, only a small number of them will develop lymphoma. An important study investigated and proposed a useful instrument for stratification of risk factors for lymphoproliferation in these groups of patients. Patients with at least two additional risk factors,

among four (Cg, low C4, leukopenia, anti-La positivity), are at high risk of lymphoma development [14]. Cg and CV occurred in 7–15% and 3–7% of patients with SS [14], respectively. According to the classification criteria for CV, a large majority of CV are HCV positive, while SS is the most common condition in HCV-unrelated CV [15]. A recent study of patients with SS and CV showed that first CV manifestations had begun in approximately 60% of patients within the first year from the SS onset, particularly with a high prevalence of CV, while other non-specific clinical manifestations such as arthralgia, myalgia, arthritis, or Raynaud's phenomena usually precede. One-third of associated NHL cases occurred during the first five years after CV onset, but diagnosis of NHL for the majority of patients was delayed, in some instances even for 20 years since CV diagnosis [16]. The presence of skin purpura has been reported as a key prognostic marker of lymphoma development in SS. Recent analysis confirmed a stronger association between patients with CV and lymphoma (hazard ratio = 7.47) than in those without CV (hazard ratio = 2.56) [17]. Approximately 10% of SS patients with MG had a hematologic malignancy, and MG increases the risk of developing either myeloma or, to a lesser extent, lymphoma [18]. There are attempts to determine and define subtype-specific predisposing factors for different subtypes of B-cell lymphoma in patients with SS. Several authors researched risk factors for developing MALT lymphoma in patients with SS. From a clinical point of view, the most important factors were Cg, higher focus score, and total ESSDAI at the time of SS diagnosis [19]. According to the World Health Organization classification, marginal zone B-cell lymphoma is classified into four subtypes: extranodal marginal zone lymphoma or MALT, primary cutaneous marginal zone lymphoma, nodal marginal zone lymphoma, and pediatric marginal zone lymphoma [20]. MALT lymphoma commonly arises from mucosal organs but rarely develops in tissue sites without mucosa: liver, thyroid, breast, skin, central nervous system. Therefore, marginal zone B-cell lymphoma in the thymus is MALT. TML is very rare, accounting for only 3% of anterior mediastinum mass [21]. Recent meta-analyses reported only up to 100 cases [22]. A recent article describing the association of SS and MALT lymphoma analyzed 142 patients in the last decade. All patients were diagnosed with MALT lymphoma simultaneously, as in our patient, or after SS. MALT lymphoma was found in the parotid glands (77.5%), lungs (14.8%), thymus in only eight patients (5.6%), submandibular glands (2.1 %), and other organs [23]. Currently, there are no standard treatment protocols or guidelines for the TML in SS. A therapeutic approach should be directed toward both diseases. Surgery, chemotherapy, radiotherapy, biological drugs – rituximab alone or in combination with chemotherapy has been commonly used [24, 25]. Some authors recommended active monitoring on the principle of "watch and wait" [26].

In our patient with clinical SGE and CV, laboratory findings of Cg and MG raised suspicion of lymphoma development. Hence, additional extensive diagnostic methods were performed, and TML was detected. Treatment with corticosteroids and hydroxychloroquine and maximal thymectomy surgery led to excellent results for both SS and TML disease treatments in our patient.

Conclusion

In patients with Sjögren's syndrome and cutaneous vasculitis, with the presence of monoclonal gammopathy and cryoglobulinemia in the early course of the disease, attention should also be paid to the rare localization of the MALT lymphoma in the thymus. According to available data, our case was only one in a few Caucasian patients, as well as the first Sjögren's syndrome-associated MALT lymphoma in the thymus in our country.

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