CLINICAL OBSERVATIONS

Transformed diffuse large B-cell lymphoma of the stomach in a patient with Sjögren's disease and systemic sclerosis: case report and literature review

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This article describes a case of a transformed diffuse large B-cell lymphoma of the stomach in a patient with Sjögren's disease (SjD) and systemic sclerosis (SSc), as well as a brief review of the literature on lymphoproliferative diseases in SjD and SSc.

Keywords: *Sjögren's disease; systemic sclerosis; anticentromere antibodies; lymphoproliferative diseases; MALT lymphoma; diffuse large B-cell lymphoma; lymphoma predictors.*

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Sjögren's disease (SjD) is an autoimmune disease (AD) that affects the secreting epithelial glands, which leads to autoimmune epitheliitis, severe impairment of cellular and humoral immunity and a high risk of B-cell lymphomas [1–3]. Extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT-lymphoma) originates from a lymphoid population that is induced by chronic inflammation in extranodal sites. MZL form a group of lymphomas originating from B-lymphocytes of the marginal zone. The WHO classification identifies three different types of MZL: extranodal MALT lymphoma; splenic MZL; nodal MZL (NMZL) [4]. MALT lymphoma is the most common type of MZL and is diagnosed in 5–8% of all B-cell lymphomas. The most common localizations of MALT lymphomas are the stomach, salivary glands, skin, orbits, lungs, thyroid gland, mammary glands, intestines and liver [4]. The main target organs in SjD are the salivary and lacrimal glands, which are affected in all patients; 25% of them develop extranodal non-Hodgkin's lymphomas (NHL) in the first 10 years of the disease in the absence of pathogenetic therapy [5]. The risk of parotid MALT lymphoma is 1000 times higher in SjD than in the general population [6]. As shown by the analysis of large series of salivary MALT lymphomas patients, an association with AD is detected in 30-90% of cases, and the most common of them are SjD and secondary Sjцgren's syndrome (sSS) [5, 7, 8]. Transformation of primary MALT lymphomas into diffuse large B-cell lymphoma (DLBCL) is rare. [7, 8]. Extranodal MALT-type lymphoma (EMALT-L), NMZL, DLBCL are the most common subtypes of NHL in SjD, and most of the latter are likely to result from transformation of MALT lymphomas and NLMZ [1–3, 9, 10].

Systemic sclerosis (SSc) is a systemic AD characterized by severe fibrotic changes in the skin, internal organs and vascular disorders, as well as the secretion of a wide range of autoantibodies. In addition to diffuse and limited forms of SSc, there is a form of SSc in combination with other rheumatic diseases (rheumatoid arthritis, SjD, systemic lupus erythematosus) or individual manifestations of these diseases ("overlap-syndrome"). [11–16]. In patients with SSc, the incidence of SjD/sSS ranges from 14 to 30%, which attracts a lot of researchers' attention, given the different treatment approaches of these ADs. The increased NHL incidence in SSc and relationship with certain specific autoantibodies remain a matter of debate [11–16]. The literature describes only one case of MALT lymphoma (with localization in the stomach) in a patient with SSc and severe esophageal injury, but without clinical manifestations of SjD [17]. Another observation presents a paraneoplastic SSc developed during the treatment of salivary NHL [18], while salivary MALT lymphoma has never been reported in this disease [19]. In the literature, we also did not find data on the development of transformed DLBCL of the stomach, either in SjD or in SSc.

We present the case of a patient with a combination of SjD and SSc, complicated by the development of gastric DLBCL. Based on this clinical case, we will evaluate the relationship between SjS, SSc and lymphoproliferative diseases (LPD).

Case report

Forty-four-year-old woman was first admitted to the V.A. Nasonova Research Institute of Rheumatology with complaints of dry

mouth, enlargement of the parotid salivary glands (PSGs), paresthesia in the hands and feet, and purpura on the lower extremities.

From the patient's medical history, it is known that she has had progressive cervical caries since the age of 34, recurrent parotitis since the age of 37, puffy fingers and Raynaud's phenomenon (RP) since the age of 39, a gradual enlargement of the PSGs since the age of 40, dry eyes since the age of 41, purpura and paresthesia of the lower extremities from the age of 44. Patient's clinical and laboratory manifestations during the follow-up are presented in Table 1. The diagnosis of SjD with damage of the salivary glands (parotid sialectasia, "parotid pseudolymphoma", severe xerostomia), eyes (keratoconjunctivitis sicca – KCS, – filamentary keratitis, severe hypolacrimia), vessels (puffy fingers, RP, cryoglobulinemic purpura) and peripheral nervous system (polyneuropathy) was made. A massive enlargement of the PSGs was regarded as a manifestation of "pseudolymphoma", according to the terminology proposed by N. Talal et al. [1] for describing such SjD manifestation. The PSG biopsy was not then performed for organizational reasons. Pulse therapy with methylprednisolone and cyclophosphamide was performed, after which chlorambucil and prednisone were prescribed for a long-term use. During the treatment, we noted the disappearance of the purpura and a significant reduction in the PSG's size.

Table 1. Clinical and laboratory features during dynamic monitoring of the patient

Clinical and laboratory features/Year	1998	2001	2008	2009	2011	2012, 2014
Recurrent parotitis	+	-	-	-	-	-
PSG enlargement	+	+	+	-	-	-
Stimulated whole salivary flow (<2,5 ml/5 min)	0	1,2	0	0	0	ND
Focus score (N<1 foci/4 mm^2)	6	2	10	ND	ND	ND
Keratoconjunctivitis sicca	+	+	+	+	+	ND
Gastritis	ND	ND	+	ND	ND	+
Puffy fingers/Raynaud phenomenon	+/-	- /+	-/+	-	-	-
Cryoglobulinemic purpura	+	-	-	-	-	-
Sclerodactyly	-	-	-	-	-	-
Calcinosis/osteolysis	ND	+/+	+/+	ND	+/+	ND
Digital ulcers	-	+	-	-	-	ND
Peripheric lymphadenopathy	-	-	+	-	-	+
Intrathoracic lymphadenopathy	-	-	+	-	-	+
Splenomegaly	-	-	-	-	-	+
Lung involvement (X-ray/CT)	+/ND	+/ND	+/+	-/+	-/-	+
Bone marrow involvement	ND	ND	+	+/-?	-	+
Salivary pseudolymphoma	+	-	-	-	-	-
Salivary MALT lymphoma B-cell clonality Lymphoma recurrence	+/-? ND	ND ND	+ + ?	- +	- + -	- + +
Transformation of MALT lymphoma into DLBCL	ND	ND	?	-	-	+
DLBCL of stomach	ND	ND	Gastritis	ND	ND	+
LDH (N < 450 IU/l)	230	140	997	179	229	ND
Cruoglobulins (N – not detected)	4+	-	-	-	-	ND
ANF (N<1/160)	-	-	1/1280	1/320	1/640	ND
Ro/La-antibodies (N < 25 IU/ml)	ND	ND	-	-	-	ND
ACA (N < 10 IU/ml)	ND	ND	288	>200	>300	ND
CD19+(B-cells)	ND	ND	0,2	0	ND	ND
RTM + bendamustine	-	-	-	-	+	+
IV GC + cyclophosphamide	+	-	-	-	-	-
R-CHOP	-	-	+	-	-	CHOP
Clinical/histological/molecular remission				+/+/-	+/+/-	+/+/-

Note. ND – no data; N – normal ranges; CT – computer tomography; ANF – antinuclear factor; GC – clucocorticoids, PSG – parotid salivary gland.

On re-admission after 3 years (at the age of 47 years), patient had no puffy fingers, but she had digital scars. There was no vasculitis, but a mild PSG enlargement persisted. X-ray revealed osteolysis of the distal phalanges of the hands and calcifications, and capillaroscopy revealed an early scleroderma pattern of abnormalities. No abnormalities were found in the analyses, except for a mild increase in gamma-globulins and rheumatoid factor (RF). The diagnosis was changed to a combination of SjD with a limited SSc. We recommended the patient to continue therapy with chlorambucil and prednisone, which she did not take after discharge.

From the age of 54, the patient again began to notice a significant enlargement of PSGs and cervical lymph nodes. A biopsy of the cervical lymph node was performed: a total violation of the lymph node structure by small cell lymphoma, mainly with diffuse growth, the cellular composition is represented by small lymphoid cells with round-oval, centrocytoid, irregular nuclei, signs of plasmacytic differentiation are expressed, there are clusters of plasma cells, large cells are discretely located among the tumor infiltrate with rounded-oval nuclei with the morphology of centroblasts, signs of colonization of preexisting follicles are visualized in some areas, the morphological picture corresponds to peripheral B-cell MZL. Given the previously diagnosed "pseudolymphoma" and a significant enlargement of the PSGs (Fig. 1), a metastatic lymph node involvement was considered.

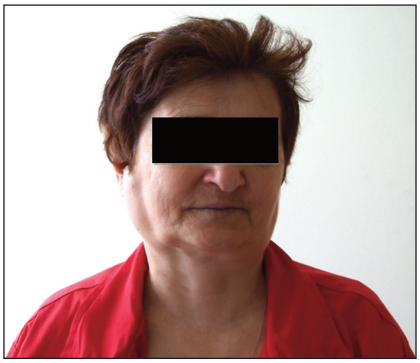

Figure 1. *Significant parotid salivary gland enlargement in patient with SjD and SSc*

A biopsy of the PSG was performed: salivary gland tissue with almost complete atrophy of the glandular parenchyma due to a "dense" lymphoid infiltrate, diffuse infiltrate with a mild tendency to nodularity, represented by small and medium-sized lymphoid cells with centrocytoid and rounded nuclei, plasmacytic cells with the morphology of monocytoid B-cells, there are many blast forms in the infiltrate, mainly of the centroblast type located discretely; immunohistochemical study revealed that tumor cells expressed CD20, BCL2, co-expressed CD43, CD27, lymphoepithelial lesions were clearly visible with pancytokeratin reaction, about 30% of tumor cells expressed the marker of proliferative activity Ki67, in some areas up to 40–50% of cells, remaining markers in tumor cells were negative; in conclusion, the morphoimmunohistochemical characteristics of the tumor infiltrate in the salivary gland correspond to MALT-type B-cell lymphoma, while at the same time, a large number of centroblasts and high mitotic activity, despite the discrete growth of blast

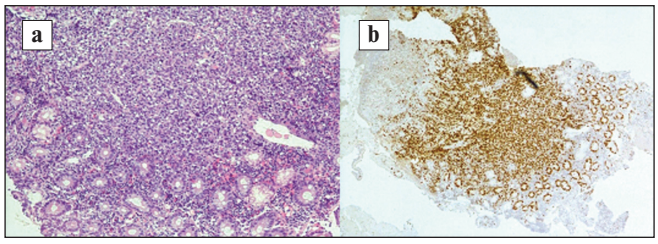

Figure 2. *Morphological examination of the stomach: a – hematoxylin and eosin staining, a fragment of the gastric mucosa with a diffuse lymphoid cell infiltrate consisting of large cells with irregularly shaped nuclei – large cell lymphoma of the stomach; b – immunohistochemical study with Ki67 staining, up to 60–70% of tumor cells are positive*

Table 2. Lymphoma predictors in Sjogren's disease

Predictors
Clinical
Significant salivary/lacrimal glands enlargement
Purpura
Lymphadenopathy
Polyneuropathy
Laboratory
Thrombocytopenia
Lymphopenia (mainly due to decrease in CD4+T-cells)
Cryoglobulinemia
Low C3/C4-complement
Paraproteinemia
Low CD19+B-cells
Morphological/molecular
Focus score >3
Significant plasma cell infiltration of salivary/lacrimal glands
Positive B-cell clonality in salivary/lacrimal glands
Predictors of transformation into DLBCL
Untreated MALT lymphoma or massive salivary/lacrimal gland enlargement
Lympadenopathy and reduction in the size of previously enlarged salivary glands (without treatment)
Foci of lymphoid infiltration in the lungs, liver, brain, etc.
Necrotizing vasculitis
Splenomegaly
B-symptoms
Paraproteinemia and BJ protein in the urine
Normalization of serum RF level (without treatment)
Hypoproteinemia with hypogammaglobulinemia
Polyclonal immunoglobulin deficiency
Salivary gland radiation therapy

Note. BJ protein – Bence Jones protein, RF – rheumatoid factor.

elements, suggest blast transformation of MALT lymphoma (initial manifestations of DLBCL?).

Gastroscopy revealed hyperemia and edema of the gastric mucosa mainly in the middle and upper third, a picture of gastritis, confirmation of tumor infiltration was not received.

Myelogram: 12% of lymphoid cells are represented by large anaplastic cells, their nuclei are round and irregular in shape with a rough chromatin structure and significant cytoplasm basophilia.

Bone marrow trephine biopsy: the bone marrow is moderately cellular, elements of all germs of hematopoiesis are visible interstitially, between them there are groups of lymphoid and plasma cells.

A combination of limited SSc and SjD, complicated by the development of disseminated MALT-lymphoma with PSG, peripheral, intrathoracic lymph node and bone marrow damage was diagnosed. Considering the presence of a generalized process, an increased level of lactate dehydrogenase, a high level of Ki-67 and the appearance of large cells in biopsy specimens, a reduced level of polyclonal IgG and a decrease of peripheral CD19+ B cells level, despite the absence of morphological confirmation of DLBCL, the patient was recommended polychemotherapy with R-CHOP. After 9 months of this therapy, when restaging with repeated PSG biopsy, complete clinical, histological/immunohistochemical remission was stated, but molecular remission was not achieved - B-cell clonality was preserved in the biopsy specimen. Maintenance therapy with rituximab (RTM) was prescribed every 3 months for 2 years.

Two years later, due to an increase in peripheral lymph nodes, a biopsy of one of them was performed, and a recurrence of NHL was recorded. Histological examination: the structure of the lymph node is disturbed due to the diffuse growth of lymphoma, along with small lymphoid cells with rounded and irregularly shaped nuclei, there are many larger lymphoid cells discretely located with blast morphology of the nuclei. Test for B-cell clonality by polymerase chain reaction (PCR) showed a positive result. Morphological confirmation of the transformation into DLBCL was not received this time either. Four courses of therapy with RTM and bendamustine followed by maintenance therapy with RTM once a month for 9 months were carried out, and clinical remission was again stated. However, after another 14 months, due to the appearance of stomach pain, a gastroscopy with a biopsy of the stomach was performed, and DLBCL was diagnosed. Morphological examination: pieces of the gastric mucosa with the development of large cell lymphoma, tumor cells express CD79α, PAX5, up to 50% of cells express FOXP1, 60–70% of cells express a marker of proliferative activity Ki67, other markers, including CD20, are negative in tumor cells, a moderate amount of reactive CD3+ T-lymphocytes in tumor

tissue, morphoimmunohistochemical characterization of tumor cells in the gastric mucosa corresponds to DLBCL (Fig. 2). The patient underwent 6 cycles of chemotherapy, repeated restaging recorded clinical and histological remission of DLBCL. However, after achieving remission, the patient died, the cause of death remained unknown.

Discussion. Currently, hematological malignancy is becoming the main cause of death in SSc and SjD, its frequency among the causes of death reaches 10% and 40–50%, respectively [19–26]. After the first reports of an increased incidence of NHL in patients with SjD [27, 28], a large number of studies have been published confirming the prevalence of predominantly B-cell NHL in this disease [1–3, 23, 24, 29]. Early studies showed that the risk of malignant lymphomas in patients with SjD was 44 times higher than in the healthy population, while the risk in patients with significant enlargement of the PSGs was 66.7 times higher, while without their enlargement – 12.5 times [27]. A high frequency of serum monoclonal immunoglobulins (mIg) and k / ƛ-chains of mIg in urine, the presence of mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor (RF) in biopsy specimens of the salivary glands in this disease were established [1, 9, 30, 31]. DLBCL and plasma cell dyscrasias were common in early studies of NHL in SjD [1–3], while massive salivary gland enlargement in this disease was characterized as "pseudolymphoma" [1, 32]. After the description of lymphomas associated with mucosal lymphoid tissue (MALT lymphomas) and the introduction of safe incisional biopsies of enlarged parotid/submandibular salivary glands, lacrimal glands, it became clear that the previously described "pseudolymphomas" were MALT-lymphomas in 70% of cases [33, 34]. The frequency of NHL in SjD in the first 10 years of the disease increased from 4–11% to 16–25%, mainly due to the diagnosis of MALT lymphomas in target organs: salivary/lacrimal glands [1–3, 5, 10, 33, 34]. This type of lymphoma has become the predominant variant of NHL in patients with SD. To use rational treatment regimens for this category of patients, various clinical, biological and morphological predictors of the lymphoma development in SjD were developed (Table 2) [35–45]. According to our case report and earlier studies, low levels of CD19+ B cells in peripheral blood can become a new serological predictor of the lymphoma development in SjD [35–37].

Although salivary MALT lymphomas are 1000 times more common in SjD than in the general population, gastric MALT lymphomas are rarely described in this disease and, unlike primary gastric MALT lymphomas, are generally not associated with Helicobacter pylori infection [46, 47]. Various pathogenetic mechanisms for the lymphoma development in SjD are presented in the literature [8, 41–45, 48]. Massive stimulation with specific autoantibodies during a long course of the disease is the main factor in the lymphoma development in ADs, while in primary MALT lymphomas, stimulation of autoreactive B-cells is caused by specific infectious agents: *Helicobacter pylori*, *Chlamydophila psittaci*, *Borrelia burgdorferi*, *Campylobacter jejuni*, *Achromobacter xylosoxidans*. Therefore, the pathophysiological mechanisms and approaches to the treatment of primary NHL and NHL associated with ADs may differ significantly [8, 47, 48].

Early epidemiological studies suggested an increased incidence of NHL in SSc, but subsequently this hypothesis was not supported by well-designed studies [6]. Among 66 cases of NHL in SSc described in the literature up to 2017, only one gastric MALT lymphoma and no case of salivary MALT lymphoma were found [19]. The frequency of NHL detection significantly increases with the combination of SjD and SSc, which was the reason to identify a special form of limited SSc in combination with SjD and anticentromere autoantibodies (ACA), associated with a high risk of NHL development [12, 16].

In our long-term follow-up of a patient with a limited SSc in combination with SjD, a multi-stage process is clearly traced: PSG enlargement with the probable development of MALT lymphoma, the subsequent development of disseminated MALT lymphoma of the salivary glands, lymph nodes, bone marrow, and then transformation into DLBCL with stomach damage. The clinical manifestations observed in our patient at the first examination are similar to those in a SjD patient described by P.E. Queneau et al. [46], who simultaneously had PSG MALT-lymphoma and stomach MALT-lymphoma in the absence of any gastrointestinal complaints at the time of the examination. Interestingly, in both cases, gastroscopy revealed chronic gastritis, but the use of endoscopic ultrasonographic guided biopsy allowed P.E. Queneau et al. [46] to diagnose stomach MALT-lymphoma with simultaneous detection of PSG MALT-lymphoma. In our patient, gastric DLBCL was diagnosed only 6 years after disseminated MALT lymphoma, which was characterized by a clinical, histological, but not molecular response to R-CHOP and RTM with bendamustine. At the onset of the disease and at the first examination at our institute, she had almost all the main predictors of the lymphoma development. The lack of therapy for localized MALT lymphoma led to a disseminated process, and then to the transformation of indolent lymphoma into DLBCL. Previously, before the development of diagnostic protocols for indolent salivary MALT-lymphomas and in the absence or insufficient therapy of SjD, we observed a high incidence of transformed highly aggressive DLBCL with a fatal outcome in most cases, despite ongoing therapy [9, 23, 28, 39, 40]. Although we have not conducted molecular studies that could clearly confirm the transformation of salivary MALT-lymphoma into disseminated MALT-lymphoma and further into gastric DLBCL, the presence of similar B-cell clone peaks in biopsy specimens during dynamic observation suggests such a mechanism for the formation of DLBCL, but not occurrence of gastric DLBCL de novo. Another possible variant of the DLBCL development in SjD patients and previously established MZL may be associated with the activation of a latent Epstein-Barr virus infection during chemotherapy and was also described by us earlier [49]. The presence of a full range of lymphoma predictors, progression and insufficient therapy in the first 15 years of SjD, the absence of molecular remission after chemotherapy of disseminated MALT lymphoma led to the development of transformed gastric DLBCL in the patient. There was no progression of SSc throughout the course of the disease. The presented clinical case shows that the NHL development in patients with a combination of SjD and SSc is associated with the progression of SjD, but not SSc, and even in the presence of complete clinical, histological/immunohistochemical remission of NHL, but in the absence of molecular remission, a high risk of subsequent relapses remains.

MALT lymphoma is the most common type of MZL and accounts for 5–8% of all B-cell lymphomas [48]. Primary extranodal salivary and stomach MZL are predominantly localized and rarely disseminated, and transformation to DLBCL occurs in less than 10% of cases [7, 8]. On the contrary, salivary MALT-lymphomas that develop in patients with AD are disseminated in 30% of cases with damage to other salivary glands, orbit, thyroid gland, stomach, lungs, lymph nodes, bone marrow, and are often accompanied by transformation into DLBCL [42, 44, 45, 48]. Studies conducted

in hematology centers have shown the presence of AD in 30–40% of patients with salivary MZL [7, 8, 47], however, MZL, DLBCL are the most common NHL in SjD, RA and SLE. In rheumatological cohorts of patients, especially those with SjD, the proportion of salivary MZL among all lymphomas reaches 60–85%, while primary salivary MALT-lymphomas that are not associated with SjD occur in no more than 10–15% of cases [5, 24, 26, 33, 50]. The MALT Lymphoma working group recommends salivary gland ultrasonography, ANF and anti-Ro/La-antibodies as standard methods for identifying association with SjD [8].

Although the use of antilymphoproliferative drugs in the early stages of SjD objectively slows down the progression of glandular/extraglandular manifestations of the disease, significantly reduces the risk of lymphoma development, and increases the survival rate of patients [3], only glucocorticoids, aminoquinoline and cytotoxic drugs (methotrexate, azathioprine, mycophenolate mofetil) are used in real practice, which may be less toxic, but do not stop the progression of the disease and do not prevent the development of NHL in SjD [26]. Early diagnosis and early anti-lymphoproliferative/anti-B-cell therapy in SjD, using of enlarged salivary/lacrimal glands biopsy to verify MALT lymphomas before the treatment, and control of B-cell clonality when re-staging the lymphoma can prevent the development of transformed B-cell NHL and improve prognosis in SjD.

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