Clonal relationship of marginal zone lymphoma and diffuse large B-cell lymphoma in Sjogren's syndrome patients: case series study and review of the literature

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Abstract

The occurrence of diffuse large B-cell lymphoma (DLBCL) in the course of Sjogren's syndrome (SS) is considered to be equally related either to the development of DLBCL de novo or to the transformation from marginal zone lymphoma (MZL). However, the question of possible clonal relationship between MZL and DLBCL in the group of SS patients remains open. Here we present the data concerning 194 patients with lymphoma complicated SS followed up at Nasonova Research Institute of Rheumatology during the last 22 years. Molecular analysis of tumor cells was performed for 6 SS patients who had developed both MZL and DLBCL. To assess clonal relationship between each of the tumor pairs immunoglobulin heavy chain (IGH) gene rearrangements were identified according BIOMED-2 protocol by means of multiplex polymerase chain reaction followed by GeneScan fragment analysis. Despite different localization MZL and DLBCL were clonally related in five tumor pairs. The median time to transformation was 11 months (range 0–78 months). MZL and DLBCL were clonally related in most cases from our cohort of SS patients. No statistically significant difference in survival between patients with DLBCL transformed from MZL and patients with de novo DLBCL was found in the cohort of SS patients investigated.

Keywords Gene rearrangement · Immunoglobulin heavy chains · Marginal zone lymphoma · Mucosa-associated lymphoid tissue lymphoma · Diffuse large B-cell lymphoma · Sjogren's syndrome

Introduction

Sjogren's syndrome (SS) is a systemic autoimmune rheumatic disease (SARD) associated with an increased risk of lymphoma [1, 2]. Among SS-associated lymphomas the most common histological types are the marginal zone

lymphoma (MZL), especially the parotid gland mucosa-associated lymphoid tissue (MALT) lymphoma, and the diffuse large B-cell lymphoma (DLBCL) [3–8].

Unlike with parotid gland MALT lymphoma the putative mechanisms lying behind the association of DLBCL with SS are still not well understood [9–11]. DLBCL can develop

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de novo or as a result of the transformation from low-grade (indolent) lymphoma. Three types of MZL according to the sites involved are defined according to the latest 2016 World Health Organization (WHO) classification: extranodal MZL of MALT (commonly termed MALT lymphoma), nodal MZL (NMZL), and splenic MZL (SMZL) [12]. Histologic transformation to a DLBCL can occur in all types of MZL [13].

Histological criteria for the transformation of MZL into DLBCL are not well outlined. Most authors noted sheets of large cells or clusters of at least 20 large cells to be the marker of transformation into DLBCL [14–17]. While others defined transformed cases to have more than 30–50% of diffusely scattered large tumor cells [18, 19].

Two conditions might be regarded as MZL to DLBCL transformation in the routine clinical practice. The first is the appearance of solid or sheet-like proliferation of centroblast-like or immunoblast-like cells in a biopsy sample in addition to the areas that meet standard morphological criteria of MZL. Second applies to DLBCL developing in the patient with previously diagnosed MZL. However, the assumptions about MZL and DLBCL clonal relationship based exclusively on the histological data are rather controversial in general and might have limited probative value for gastric lymphoma only [16, 20–25].

This study is aimed to investigate possible clonal relationship between MZL and DLBCL developed in the patients with SS.

Materials and methods

We searched the files of the V.A. Nasonova Research Institute of Rheumatology (Moscow, Russia) from June 01, 1997 until June 01, 2019 for MZL cases with synchronous or metachronous DLBCL complicating SARD at diagnosis or later. Inclusion criteria were: over 18 years of age, availability of medical records confirming the SARD diagnosis, biopsy-proven MZL with synchronous or metachronous biopsy-proven DLBCL, and the availability of paraffin blocks for molecular analysis.

All MZL lymphomas and DLBCLs were identified by the surgical biopsy of a lymph node or extranodal tissue (except for the bone marrow). The tissue specimens were fixed in 10% formalin, routinely processed, and embedded in paraffin. The original hematoxylin and eosin (H&E)-stained slides were prepared for all cases.

Immunohistochemical studies with a panel of B- and T-cell markers were carried out on the formalin-fixed paraffin-embedded (FFPE) tissue. The antibodies used in the immunohistochemical studies, diluted as suggested by the manufacturers, are presented in Table 1. After dewaxing and heat-induced antigen retrieval, sections were stained

Table 1 Antibodies used in the immunophenotypic analysis

Antibody	Clone	Source
CD2	MRQ-11	Cell Marque, Rocklin, CA
CD3	F7.2.38	Dako, Glostrup, Denmark
CD10	56C6	Cell Marque
CD20	L26	Dako
BCL6	EP278	Cell Marque
MUM1	MRO-8	Cell Marque
PAX5	DAK-Pax5	Dako
Ki-67	SP6	Cell Marque

using Autostainer Link 48 (Dako, Denmark) according to the manufacturer's instructions.

In one of our cases (Case 6), the morphologically distinct tumor components were microdissected to determine the clonal relationship between the MALT lymphoma and DLBCL components.

DNAs from FFPE samples were extracted as described in [26]. The BIOMED-2 primer set and standardized protocol were used to study immunoglobulin heavy chain (IGH) gene rearrangements [27]. IGH framework (FR) 1, 2, and 3 assays (Tube A, Tube B, and Tube C, respectively) were used to reveal V_H-J_H rearrangements. The fragments were detected on an ABI PRISM 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA) and the data were analyzed with GeneMapper software version 4.0 (Applied Biosystems, Foster City, CA).

Overall survival was estimated by the Kaplan–Meier method and was calculated as the time from the DLBCL diagnosis until death or the last follow up. Log-rank test was used to compare overall survival between the groups of patients with DLBCL transformed from MZL and de novo DLBCL.

Results

We identified 169 patients with MZL and 25 patients with DLBCL complicating SARD diagnosed in our hospital during the 22-year interval. Six of these patients had two lymphomas: MZL and synchronous or metachronous DLBCL (Table 2). All six patients were women, median age 61 years (range 54–73 years) at the time of MZL diagnosis and had SS alone (Cases 1–4) or in association with limited cutaneous systemic sclerosis (Case 5) or with rheumatoid arthritis (Case 6). Cases 1 and 6 also had Hashimoto's thyroiditis. Based on the full staging evaluation, in five cases, the diagnosis was established as extranodal MZL of MALT type, and in one case, NMZL (Case 4). MALT lymphoma was found in the salivary gland in four cases and in the bronchial wall in one case. The proliferation fraction was measured by

Table 2 Summary of clinical findings of six cases

Case no./sex	Age at MZL	Rheumatological diagnosis	MZL tissue specimen	MZL Ki-67 (%)	DLBCL subtype (Hans algorithm)	DLBCL tissue specimen	Time from MZL to DLBCL (months)	MZL and DLBCL clonal relationship
1/F	56	pSS + HT	Parotid gland	ND	Non-GCB	Stomach	32	Yes
2/F	62	pSS	Bronchial wall, lymph node	10	Non-GCB	Lung	11	Yes
3/F	73	pSS	Parotid gland, lymph node	40–50	GCB	Retroperitoneal area	Simultaneously	Yes
4/F	60	pSS	Lymph node	40	Non-GCB	Soft tissue in mandibular fossa	8	Yes
5/F	54	limited cutaneous SScI + sSS	Parotid gland, lymph nodes	40–50	GCB	Stomach	78	Yes
6/F	63	RA + sSS + HT	Left parotid gland	7	Non-GCB	Left parotid gland	Simultaneously, composite lymphoma of the left parotid gland	Not

MZL marginal zone lymphoma, DLBCL diffuse large B-cell lymphoma, pSS primary Sjögren's syndrome, sSS secondary Sjögren's syndrome, HT Hashimoto's thyroiditis, SScI systemic sclerosis, RA rheumatoid arthritis, GCB germinal center of the B-cell subtype, ND not determined

Ki-67 antibodies and was unusually high for MZL in three out of four cases (Cases 3–5) (Fig. 1), ranging from 40 to 50%. In two patients (Cases 3 and 6), DLBCL was diagnosed

simultaneously with MZL, and in four cases (Cases 1, 2, 4, and 5), 8–78 months after MZL. In all cases except for Case 6, the location of DLBCL was different from that of MZL. In

Fig. 1 Cases of MZL with a high proliferative activity index. Case 3. The parotid salivary gland affected by MALT lymphoma. **a** Hematoxylin and eosin (H&E) stains, **b** Ki-67; Case 4. The lymph node

affected by MZL. **c** H&E stains, **d** Ki-67; Case 5. The parotid salivary gland affected by MALT lymphoma. **e** H&E stains, **f** Ki-67; All photomicrographs original magnification $\times 400$

Case 6, composite lymphoma (MALT lymphoma/DLBCL) of the parotid gland was diagnosed. In three patients (Cases 1, 3, and 4), the DLBCL was confined to extranodal sites, and other three patients (Cases 2, 5, and 6) presented with nodal and extranodal DLBCL.

Immunohistochemical subtyping of DLBCLs according to the Hans algorithm was performed for all cases [28]. Based on their expression patterns, two cases of DLBCL were allocated to the germinal center of the B-cell (GCB) subtype and four cases into the non-GCB subtype.

Monoclonal rearrangement of the IGH gene was detected in both specimens for all six tumor pairs. The results of the IGH clonality analysis for six paired samples of MZL and DLBCL are presented in Table 3. Identical clonal patterns of MZL and DLBCL were observed in five tumor pairs (Cases 1–5), showing the clonal relationship of the tumors in these cases. In Case 6, fragment analysis of the frame region 3 by polymerase chain reaction (PCR) products from

microdissected MALT lymphoma and DLBCL components showed different clonal pattern rearrangements of the IGH gene.

To assess whether patients with SS-related DLBCL transformed from MZL (5 patients) have a worse prognosis compared with patients with de novo SS-related DLBCL (17 patients), we compared overall survival in both groups. We did not find any statistically significant difference in survival between these groups ($p = 0.139$) (Fig. 2).

Search strategy

We performed a literature search in Medline, Scopus and Web of Science up to March 2019, according to the published guidance [29]. We used the following keywords: “Sjögren’s syndrome”, “lymphoma”, “mucosa-associated lymphoid tissue lymphoma”, “diffuse large B-cell lymphoma”, and “transformation” to identify the relevant

Table 3 Results of IGH clonality analysis for six paired samples of marginal zone lymphoma and diffuse large B-cell lymphoma

	No 1		No 2		No 3		No 4		No 5		No 6	
	MZL	DLBCL	MZL	DLBCL	MZL	DLBCL	MZL	DLBCL	MZL	DLBCL	MZL	DLBCL
V_H-J_H (FR1)	338	338	325	NA	325	326	327	327	328	328	NA	NA
V_H-J_H (FR2)	272	272	265	265	266	266	268	268	268	268	NA	283
V_H-J_H (FR3)	poly	poly	124	124	125	125	127	127	128	128	108	131

IGH immunoglobulin heavy chain, FR framework, NA no amplification, MZL marginal zone lymphoma, DLBCL diffuse large B-cell lymphoma, poly polyclonal

Fig. 2 Overall survival curves for SS patients with DLBCL transformed from MZL and with de novo DLBCL

Table 4 Review of literature on the MALT lymphoma transformation to the DLBCL in patients with Sjogren's syndrome

Study	Number of Cases	Age ^a /sex	MALT lymphoma localization	Time from MALT lymphoma to DLBCL (months)	DLBCL localization	MALT lymphoma and DLBCL clonal relationship
Solans-Laqué et al. [37]	2	68/F	PG	NA	NA	ND
		67/F	PG	NA	NA	ND
Royer et al. [4]	1	60/M	Bronchus	10	Retroperitoneal lymph nodes	Yes
Biasi et al. [38]	1	64/F	Salivary glands	84	PG	ND
Ramos-Casals et al. [39]	2	65/F	PG	60	NA	ND
		59/F	PG	24	NA	ND
Voulgarelis et al. [34]	1	48/F	NA	36	NA	ND
Vasaitis [35]	3	NA	NA	NA	NA	ND
Strunk et al. [36]	1	42/F	PG	Simultaneously, EBV-driven transformation	Liver, lung, kidney, bone marrow, lymph nodes	Yes

MALT mucosa-associated lymphoid tissue, *DLBCL* diffuse large B-cell lymphoma, *PG* parotid gland, *EBV* Epstein–Barr virus, *NA* not available, *ND* not determined

^aFor the time of MALT lymphoma diagnosis

original articles, letters to the editor, and case reports published in English. There were no exclusion criteria.

Discussion

In this study, we investigated the clonal relationship between low- and high-grade lymphomas in six patients with SS. In all cases, low-grade lymphoma was classified as NMZL or MALT lymphoma. Both MZL subtypes are the most common histological type of lymphoma developing in SS patients. MZLs have the potential to progress into a more aggressive histologic type, predominantly in DLBCL [18, 30–32].

Histologic transformation of MALT lymphoma and NMZL is, according to Conconi and colleagues, observed in 4% and in 3% of patients, respectively, with the median time for transformation being 32 months (range 12–144 months) after diagnosis of MZL [31]. Maeshima and colleagues reported the histological transformation of MALT lymphoma into DLBCL in 8% of their patients, with the median time to the transformation of 48 months (range 2–139 months) after the MALT lymphoma diagnosis [18]. In our cohort, the transformation of MZL into DLBCL was observed in 3% of patients and median time to transformation was 11 months (range 0–78 months).

The emergence of DLBCL in the course of SS could be equally attributable either to the development *de novo* or to the transformation from MZL. After reviewing all the relevant literature, we found 14 cases of SS and DLBCL with morphological signs showing the origin of DLBCL from MZL: 11 cases from MALT lymphoma and 3 cases from NMZL [4, 33–35]. In 11 additional cases, DLBCL was

diagnosed either concurrently with MZL (but in a different location) or 10–84 months after the MALT lymphoma diagnosis (Table 4) [4, 34–39]. Royer and colleagues reported a DLBCL case diagnosed in the retroperitoneal lymph nodes 10 months after the initial bronchial MALT lymphoma in a 60-year-old man with SS [4]. In both lymphomas, *t*(14;18) was detected, strongly suggesting their clonal relationship. Strunk and colleagues described a case of a rapidly progressing Epstein–Barr virus-driven transformation of parotid gland MALT lymphoma into DLBCL with liver, lung, kidney, bone marrow, and lymph nodes involvement in a 42-year-old female patient with SS [36]. MALT lymphoma and DLBCL in this case had identical IGH rearrangement profiles. However, other cases had not been studied using molecular methods to establish their clonal relationship.

In our group, the fragment analysis showed identical clonal IGH gene rearrangement patterns between the MZL and DLBCL in each of the five tumor pairs (Cases 1–5), indicating the clonal identity of the two lymphomas. In all these cases, low- and high-grade lymphomas had different localization. In only one patient (Case 6), both lymphomas (DLBCL and MALT lymphoma) were detected in the same location, which initially led us to the erroneous conclusion that DLBCL results from MALT lymphoma progression. However, the fragment analysis showed different clonal IGH gene rearrangement patterns from microdissected MALT lymphoma and DLBCL components, showing that these lymphomas are not clonally related.

The Ki-67 proliferation index is low in MZL [40]. Three of our four cases of MZL with the subsequent transformation into DLBCL had a high index of proliferative activity of tumor cells (Table 2). The Ki-67 proliferation index was not used to diagnose the transformation to DLBCL given

the lack of an agreed cutoff for this distinction [17]. However, Petit and colleagues showed that the increase in Ki-67 expression in MZL is an independent parameter associated with a worse outcome [41]. Considering the results of our study, we think that further research is needed to decide whether the high proliferative activity index of tumor cells in MZL is a risk factor for MZL transformation. The small number of cases and the retrospective nature of the study did not allow us to identify risk factors for the transformation of MZL into DLBCL in patients with SS.

We suggest that in SS patients with both MZL and DLBCL these tumors are usually clonally related, which most likely shows that high-grade DLBCL emerged from low-grade MZL. Patients with MZL, therefore, need to be closely monitored by a physician for timely diagnosis of the high-grade DLBCL. We are confident that estimates whether DLBCL results from low-grade B-cell lymphoma progression should only be done based on molecular analysis of tumor clones even in the cases with histological features suggesting such transformation.

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Author contributions VRG collected samples, collected clinical patient data, analyzed data, took part in study design, performed the statistical analysis, and wrote, edited, and reviewed the manuscript. NAP and SGR-L performed histopathological and immunohistochemical examinations, took part in study design, substantially contributed to the interpretation of the data, edited and reviewed the manuscript. NVR and YVS collected samples, performed molecular studies, took part in study design, substantially contributed to the interpretation of the data, edited and reviewed the manuscript. ABS: took part in study design, substantially contributed to the interpretation of the data, edited and reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the V.A. Nasonova Research Institute of Rheumatology Ethics Committee, reference number 19/18 on the 29/11/2018.

Informed consent Informed consent was obtained from the patients included in the study.

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