T cell lymphoma in the setting of Sjögren's syndrome: T cells gone bad? Report of five cases from a single centre cohort

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ABSTRACT

Objective. *To identify and record lymphomas of T cell origin in a single centre cohort of 110 Sjögren's syndrome (SS)-associated non-Hodgkin's lymphoma (NHL) patients, followed up from 1993 to June 2020.*

Method. *We searched for patients diagnosed with T cell lymphoma among 110 SS-associated NHL cases. Demographic data, history of previous lymphoma, histologic subtype, lymphoma stage, treatment schedules, and response to therapy were documented.*

Results. *Among the 110 SS-associated NHL patients, we identified five NHL cases of T cell origin, all of whom were women. The median time from SS diagnosis to T cell lymphoma development was 3.25 years. They all expressed at least one adverse predictive factor for lymphoma development. Lymphoma subtypes were identified as: two peripheral T cell lymphomas not otherwise specified (NOS) lymphomas, one primary cutaneous T cell lymphoma, one T large granular lymphocyte (T-LGL) leukaemia and one angioimmunoblastic T cell lymphoma. All lymphomas were stage IV, apart from the latter case that was stage III, according to the Ann Arbor staging system. All lymphomas tested positive for T cell receptor (TCR) gamma clonal rearrangements in biopsy specimens, and two were also positive for Epstein-Barr virus-encoded RNA (EBER). Two out of five patients had previously been diagnosed with B cell lymphoma, treated with combined immunochemotherapy, and one had been previously diagnosed with lymph node benign polyclonal follicular hyperplasia.*

Conclusion. *SS-associated T cell lymphomas constitute a minority. Treatment with anti-CD20 monoclonal antibody (mAb) and viral infections may be implicated in their pathogenesis.*

Introduction

Sjögren's syndrome (SS) bears the highest risk for lymphoma development among autoimmune diseases (1). Lymphomas in this setting are mainly of B cell origin with mucosa associated lymphoid tissue (MALT) lymphomas constituting the majority (2). SS-associated T cell lymphomas are rare with only single cases having been reported in the literature to date (3). Herein, we present five lymphoma cases of T cell origin recorded in a cohort of 110 SS-non-Hodgkin Lymphoma (NHL) patients followed up in the Pathophysiology Department of National and Kapodistrian University of Athens from 1993 to June 2020, and we comment on the possible implicating factors.

Case 1

In April 2002, a 52-year-old Caucasian woman with a 2-year history of SS presented with B symptoms, peripheral lymphadenopathy and non-pruritus skin lesions. Cervical lymph node, bone marrow (BM) and skin lesion histology revealed diffuse infiltration by predominant small, medium and large lymphocytes expressing T cell receptor (TCR) gamma chain gene clonal rearrangement and $CD45R0^+$, $CD3^+$, $CD4^+$ phenotype, indicative of peripheral T cell lymphoma not otherwise specified (NOS). The lymph node specimen was also Epstein-Barr Virus-encoded RNA (EBER)-positive. The patient received eight cycles of cyclophosphamide-hydroxydaunorubicin-vincristine-prednisone (CHOP), with subsequent partial remission (PR). Therefore, salvage chemotherapy with four cycles of etoposide-methylprednisolone-high-dose cytarabine-cisplatin (ESHAP) followed, leading to complete remission (CR). Four years later, mild hepatosplenomegaly was noted during routine follow-up; abdominal computed to-

mography (CT) revealed the presence of nodular liver lesions. Liver and BM biopsy histology was compatible with stage IV Hodgkin lymphoma. The patient received 11 adriamycin-bleomycin-vinblastine-dacarbazine (ABVD) cycles, followed by lymphoma CR. The patient is alive and remains in CR.

Case 2

In October 2007, a 42-year-old Caucasian woman with a 10-year history of SS complicated with membranoproliferative glomerulonephritis, sensory peripheral neuropathy, type II cryoglobulinaemia and palpable purpura of lower extremities, presented with mild bilateral parotid gland enlargement and anaemia. A lymphoproliferative disorder was suspected. Evaluation for lymphoma revealed marginal zone lymphoma (MZL) of the BM and salivary gland. Starting in October 2007, she received 3 monthly cycles of anti-CD20 monoclonal antibody (mAb) Rituximab (R)at 6-month intervals which resulted in CR. Lymphoma relapse occurred in July 2009, and again in June 2010. In both instances, the patient received combined immunochemotherapy chemotherapy with R-CHOP and bortezomib-dexamethasone-R regimen respectively, achieving CR. The patient was monitored at 3-month intervals.

In February 2013, she was urgently admitted due to sub-acute flaccid paralysis of the upper and lower extremities. Neurological examination also revealed right Babinski and Brutzinski sign. Magnetic resonance imaging (MRI) of the brain and spine was consistent with pachymeningitis and pituitary gland infiltration. Cerebrospinal fluid analysis disclosed the presence of $CD3^+$ T lymphocytes expressing TCR gamma chain gene clonal rearrangement. Central nervous system (CNS) lymphoma was suspected. A brain biopsy was not performed due to increased risk of adverse events. Full body CT was negative for lymphadenopathy and hepatosplenomegaly. BM and salivary gland histology exhibited infiltration by T lymphocytes with a $CD3^+$, $CD4^-$, $CD8^+$, $CD5^+$, $CD7^+$, $CD56^-$, $CD57^-$ phenotype and TCR gamma gene clonal rearrangement, compatible with peripheral T cell lymphoma NOS. Although not histologically proven, CNS was also considered to be affected.

Salvage chemotherapy with ESHAP regimen was applied, and the patient underwent autologous stem cell transplantation. She is currently alive and in CR.

Case 3

In April 2010, a 76-year-old Caucasian woman with a 2-year history of SS presented with a fixed right parotid gland enlargement. She was diagnosed with stage IV MZL involving the salivary gland and bone marrow. Starting in April 2010, she received four monthly pulses of combined immunochemotherapy with anti-CD20 mAb rituximab and fludarabine. Re-evaluation after therapy completion revealed CR and the patient was monitored at 3-month intervals. Sixteen months after NHL diagnosis, a routine complete blood count (CBC) indicated pancytopenia. Lymphoma relapse was suspected, and BM biopsy was performed. BM histology revealed interstitial infiltration by small T lymphocytes expressing TCR gamma chain gene clonal rearrangement and $CD3^+$, $CD4^+$, $CD8^+$, $CD57^+$, $CD56^-$ phenotype, findings consistent with T Large Granular Lymphocyte (T-LGL) leukaemia. Oral cyclosporine resulted in the reinstatement of normal haemopoiesis.

In February 2013, the patient was diagnosed with B cell lymphoma transformation to diffuse large B cell lymphoma (DLBCL)of the lymph nodes and lung. She refused treatment and died a few months later due to bulky disease.

Case 4

In May 2010, a 61-year-old Caucasian woman with a 2-year history of SS presented with a single palpable maculopapular skin lesion of the left nasomalar furrow. Physical examination revealed mild splenomegaly while CBC and biochemical profile were normal. Surgical excision and biopsy of the lesion revealed nodular infiltration of the dermis and subcutis, without epidermotropism, by small and medium size lymphocytes expressing TCR gamma chain gene clonal rearrangement and a $CD3^+$, $CD4^+$, $CD8^-$, $CD30^-$ phenotype compatible with primary cutaneous CD4 positive small/medium T cell lymphoma. The biopsy specimen was also EBER-positive. Lymphoma staging was completed with full body CT imaging, upper and lower GI endoscopy and BM biopsy. BM was also involved. Since this particular type of primary cutaneous T cell lymphoma exhibits indolent behaviour, a "wait and watch" policy is being applied.

Case 5

In October 2019, a 69-year-old Caucasian woman, with a 3-year history of SS, presented with bilateral axillary lymphadenopathy. Of note, she had a 20-year history of generalised small size lymphadenopathy, histologically proven to be polyclonal follicular hyperplasia by multiple lymph node biopsies. Physical examination revealed peripheral lymphadenopathy and splenomegaly, while CBC was remarkable for thrombocytopenia. Positron emission tomography (PET)/CT imaging demonstrated multiple hypermetabolic cervical, axillary, thoracic and intra-abdominal lymph nodes, as well as diffuse hypermetabolism of the splenic parenchyma. Surgical excision and biopsy of an axillary lymph node revealed diffuse infiltration by medium and scarce large lymphocytes of T-cell origin expressing TCR gamma chain gene clonal rearrangement and a $CD3^+$, $CD2^+$, $CD5^+$, $CD4^+$, $CD7^+$, $bcl\text{-}2^+$, $bcl\text{-}6^+$, $CD10^+$, $PD\text{-}1^+$, $CD20^-$, $CD8^-$ phenotype, compatible with angioimmunoblastic T cell lymphoma. Lymphoma staging included BM biopsy and GI tract endoscopy, demonstrating no lymphoma involvement. The patient received cyclophosphamide-hydroxydaunorubicin-vincristine-etoposide-prednisone (CHOEP) chemotherapy, from November 2019. Partial lymphoma remission was demonstrated after 4 cycles of CHOEP. One month after the fourth CHOEP cycle, the patient developed neutropenia and thrombocytopenia. BM biopsy was performed to exclude lymphoma infiltration. No T cell lymphoma infiltration was observed, while histology revealed a hypercellular BM with granular and megakaryocytic hyperplasia. Thus, the

Table I. Summary of the patient's characteristics.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Female	Female	Female	Female	Female
Age at lymphoma diagnosis	52	42	76	61	69
Low C4	No	Yes	Yes	No	Yes
RF	-	+	+	-	-
ANA	-	+	+	+	+
Ro/La	-/-	+/+	+/-	+/-	-/-
Disease duration from SS diagnosis to lymphoma diagnosis	2	10	2	2	3
Lymphoma type	T-Peripheral NOS	T-peripheral NOS	T-LGL Leukaemia	T-primary cutaneous	Angioimmunoblastic T cell lymphoma
Adverse lymphoma predictor	SGE	Glomerulonephritis Palpable purpura Cryoglobulinaemia Low C4	SGE Low C4	SGE	SGE Lymphadenopathy Low C4
Ann Arbor stage	IV	IV	IV	IV	III
Sites involved	Bone marrow Lymph nodes Skin	Bone marrow CNS Salivary gland	Bone marrow	Bone marrow Skin	Lymph nodes
Prior lymphoma	No	MALT	MALT	No	No
Ann Arbor stage of previous lymphoma	-	IV (BM, SG)	IV (BM, SG)	-	-
Previous immunochemotherapy	-	Rituximab R-CHOP BDR	Rituximab Fludara	-	-
EBER	Positive	No	No	Positive	No
Management	CHOP-ESHAP	ESHAP-ASCT	Cyclosporin	Active surveillance	CHOEP
Outcome	Alive in complete remission	Alive in complete remission	Death	Alive under follow-up	Alive undergoing remission evaluation

RF: rheumatoid factor; ANA: antinuclear antibodies; LGL: large granular lymphocyte; NOS: not otherwise specified; SGE: salivary gland enlargement; EBER: Epstein-Barr virus-encoded small RNAs; CNS: central nervous system; MALT: mucosa associated lymphoid tissue; BM: bone marrow; SG: salivary gland; R-CHOP: rituximab cyclophosphamide doxorubicin vincristine prednisone; BDR: bortezomib, dexamethasone, rituximab; CHOP: cyclophosphamide doxorubicin vincristine prednisone; ESHAP: etoposide methylprednisolone high dose Ara-C Platinol; ASCT: autologous stem cell transplant; CHOEP: cyclophosphamide doxorubicin vincristine, etoposide, prednisone.

patient was treated with high dose corticosteroids in the setting of immune mediated neutropenia and thrombocytopenia, with subsequent complete haematological response. She has completed 6 cycles of the CHOEP regimen and lymphoma remission evaluation is currently pending.

Discussion

SS is the prototype model for autoimmunity-related lymphoproliferation. Several studies have established a strong correlation between lymphoma development and SS, while adverse predictors for such complications as hypocomplementaemia, lymphocytopenia, cryoglobulinaemia, purpura, and salivary gland enlargement, have been successfully identified (4, 5). There are two dominant types of lymphoma in SS: MZL (extranodal MZL called MALT lymphomas and nodal MZL) and aggressive lymphomas such as DLBCL (6).

Common ground for all lymphoma subtypes in the setting of SS is that they originate from B cells. This can be attributed to the fact that the disease itself rests upon immune activation, subsequent to activation or apoptosis of glandular epithelial cells, expressed as a self-perpetuating T cell-dependent autoimmune sequel, leading to B cell deregulation. In this setting, B cell clones are selected and expanded, leading to the emergence of monoclonality which, when combined with genetic disorders, results in B cell lymphomas (7).

Although there is evidence of T cell oligoclonality in SS, as demonstrated by the restricted TCR repertoire of the infiltrating T cells in the salivary glands (8), these T cell clones do not expand, thus explaining the rarity of T cell lymphomas. Indeed, few cases of T NHL have been reported to date, with angioimmunoblastic T cell lymphomas constituting the majority (3).

Contrary to the data published so far, we identified five cases (4.5%) of T NHL among 110 SS-NHL patients. Four lymphoma subtypes were recorded: periph-

eral T cell lymphoma NOS, cutaneous T cell lymphoma, T LGL leukaemia and angioimmunoblastic T-cell lymphoma. Two out of five patients (cases 2 and 3) had been diagnosed with T cell malignancy at 16 months and 6 years, respectively, after B cell NHL diagnosis. One patient (case 5) had a 20-year history of lymph node benign polyclonal follicular hyperplasia, before T cell lymphoma diagnosis. All five patients exhibited at least one adverse predictive factor for lymphoma development. Of interest, the cases seem to share some common features: prior exposure to immunotherapy with anti-CD20 mAb (cases 2 and 3) due to previously diagnosed B cell NHL, and evidence of EBV infection (cases 1 and 4). A complete description of the case series characteristics is shown in Table I.

B cell depletion therapy with anti-CD20 mAb has significantly improved the survival of NHL patients, while its effectiveness and safety on lymphoma-related autoimmune phenomena have promoted its application in primary autoimmune diseases (9).

Recently, accumulating data have indicated potential adverse outcomes linked to B cell depletion therapy such as a paradoxical immune stimulatory effect and the emergence of T cell malignancies (10).

The impact of B cell depletion can only be understood in association with B cell properties. B cell function is not limited to antibody production; B cells are also antigen presenting cells. In the presence of various co-stimulatory molecules, antigen presentation elicits T cell assistance required for B cell maturation which, in turn, allows B cells to drive optimal T cell activation and differentiation into memory subsets. Additionally, activated B cells produce a vast range of cytokines and chemokines that modulate maturation, migration and function of other immune effectors, among which T follicular helper (Tfh) cells are of great significance since B cell and Tfh cross-talk generates and maintains the formation of germinal centres (11).Recent studies in humans have also revealed the existence of a B cell subset, characterised as $CD19^{+}$ $CD24^{hi}CD38^{hi}$B cells (Breg), which possesses a regulatory capacity. FollowingCD40 stimulation, these cells suppress the differentiation of T helper 1 cells (12). Breg interactions, identified in murine models of autoimmune diseases, are not restricted to Th1 cells. Breg activation also results in apoptosis of effector T cells, induction and activation of Treg cells and the inhibition of autoreactive T cell activation (13).

Although studies on B cell reconstitution and T helper cell balance after Rituximab treatment do not reveal numerical abnormalities of Tregs and effector T cells in the periphery (14),given the multipotent profile of B cells and the fact that some lymphoma T cells may adopt a T regulatory (Treg) cell profile (15), one could argue that disturbance of the interplay balance between B and T cells caused by B cell depletion creates a scenario whereby T cell clones select and expand, thus leading to T cell malignancy.

EBV is commonly associated with the development of some malignancies of lymphoid origin including endemic Burkitt lymphoma, EBV-positive Hodgkin lymphoma, post-transplantation lymphoproliferative disorders, and NK T cell lymphoma. It is speculated that EBV-affected cells through upregulation of chemokine expression promote the migration of Tregs to tumour lesions, and that these antigen-specific Tregs can inhibit the EBV-specific host immunity, leading to tumour progression (16). Primarily affecting B cells by interfering in their survival, differentiation and proliferation, possibly through changing Activation Induced Cytidine Deaminase (AID) expression, thereby causing genomic instability, EVB also possesses the potential to influence T cells. Recent studies indicate that EBV infection may regulate $CD8^{+}$ natural killer T (NKT) cell development in the host (17). Failure of $CD8^{+}$ NKT cells conversion could further induce functional disturbance of T cell subpopulations, eventually compromising T cell surveillance. In this setting, T cell clonality and expansion could emerge.

In conclusion, SS-related T cell lymphomas constitute a rare entity, and although a causative relationship between SS-related T cell lymphomas and anti-CD20 mAb therapy as well as EBV infection cannot be established, a possible implication should not be ignored. On the contrary, it becomes clear that SS-lymphoma patients receiving therapy should be closely monitored for potential subsequent T cell lymphoma development.

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