



## Case report

# Antiphospholipid antibodies associated with nodal marginal zone lymphoma and its progression to diffuse large B-cell lymphoma—A case report

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## ABSTRACT

An association between autoimmune events, as well as the development of antiphospholipid (aPL) antibodies and lymphoproliferative disorders is well recognized. We present the patient with coagulation abnormalities and non-Hodgkin lymphoma (NHL), primarily diagnosed as nodal marginal zone B-cell lymphoma (NMZL), and in relapse as diffuse large B-cell lymphoma (DLBCL). In the follow-up period, the patient simultaneously developed different aPL antibodies. The presence of aPL antibodies in NHL is frequent but it is not common in the NMZL. The aim of the present case report is to highlight the possible underlying increase of aPL antibodies in NMZL patients with coagulation tests abnormalities.

## 1. Background

Antiphospholipid (aPL) antibodies comprise a heterogeneous family of acquired autoimmune antibodies against anionic phospholipids and protein-phospholipid complexes [1]. The most commonly detected aPL antibodies are lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β<sub>2</sub>-glycoprotein I (anti-β<sub>2</sub>-GPI) antibodies. The presence of these antibodies is associated with antiphospholipid syndrome (APS), a systemic autoimmune disorder characterized by venous, arterial or small-vessel thrombosis, recurrent pregnancy loss, and/or thrombocytopenia [2]. Antibody positivity may be related to a wide variety of conditions including autoimmune diseases, infections, malignancies, and/or certain drugs such as procainamide, chlorpromazine and hydralazine [3,4]. However, aPL antibodies can also be detected in about 2% of the healthy population [1].

A large group of solid tumors has been reported to be associated with LA, aCL and anti-β<sub>2</sub>-GPI antibody positivity, including tumors of the breast, colon, kidney, liver and ovary [5,6]. However, a high prevalence of aPL antibodies is also reported in patients diagnosed with hematologic malignancies, e.g., acute myeloid leukemia, lymphomas, hairy cell leukemia, myelomonocytic leukemia and acute lymphoblastic leukemia [1].

Nodal marginal zone B-cell lymphoma (NMZL) is defined as

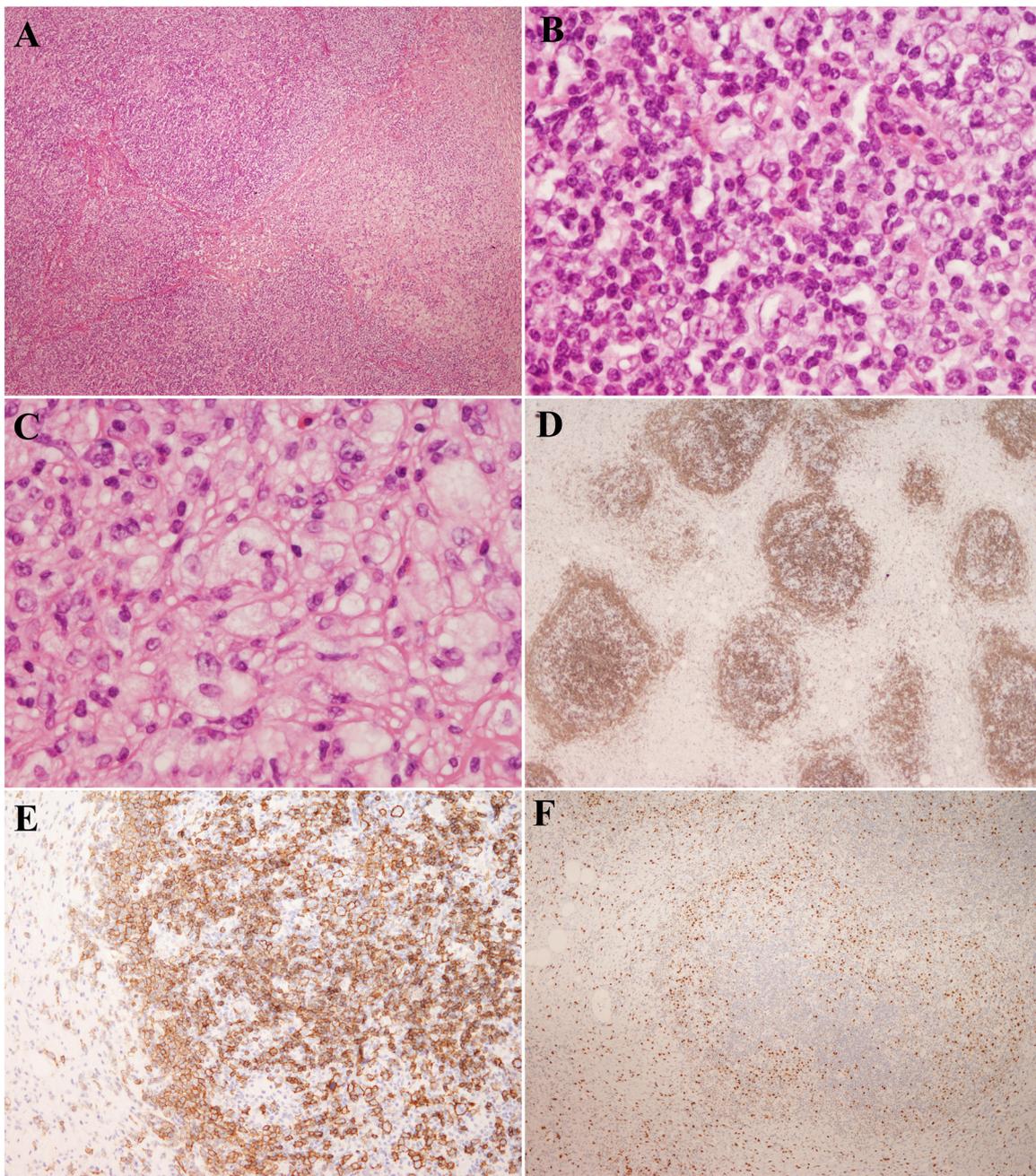
marginal zone lymphoma primarily presenting in the lymph node in the absence of clinical evidence for prior or concurrent involvement of extranodal sites (other than bone marrow) or spleen [7]. It is uncommon form of lymphoma accounting for 1.5%–1.8% of lymphoid neoplasms. However, diffuse large B-cell lymphoma (DLBCL) is an aggressive and the most common non-Hodgkin lymphoma (NHL) worldwide. The transformation of NMZL into DLBCL is considered if more than 20%, or by some authors more than 50% of cells were centroblasts [8,9]. While some diagnose transformation in DLBCL only if sheets of large cells are present, a criterion used in other lymphoma types as well [10].

There are several proposed mechanisms connected to aPL antibody production in lymphoproliferative malignancies, including aPL antibody production by malignant B-cells or by B-cells activated via cytokine secretion by malignant T-cells [11]. However it is also very plausible that reactive B-cells produce these antibodies in the context of a B-cell lymphoproliferative malignancy (reviewer's comment).

To the best of our knowledge, we report a unique case of NMZL with transformation in DLBCL with concurrent aPL antibody positivity. The presence of aPL antibodies in NHL is frequent but it is not common in the NMZL. The aim of the present case report is to highlight the possible underlying increase of aPL antibodies in NMZL patients with coagulation tests abnormalities.

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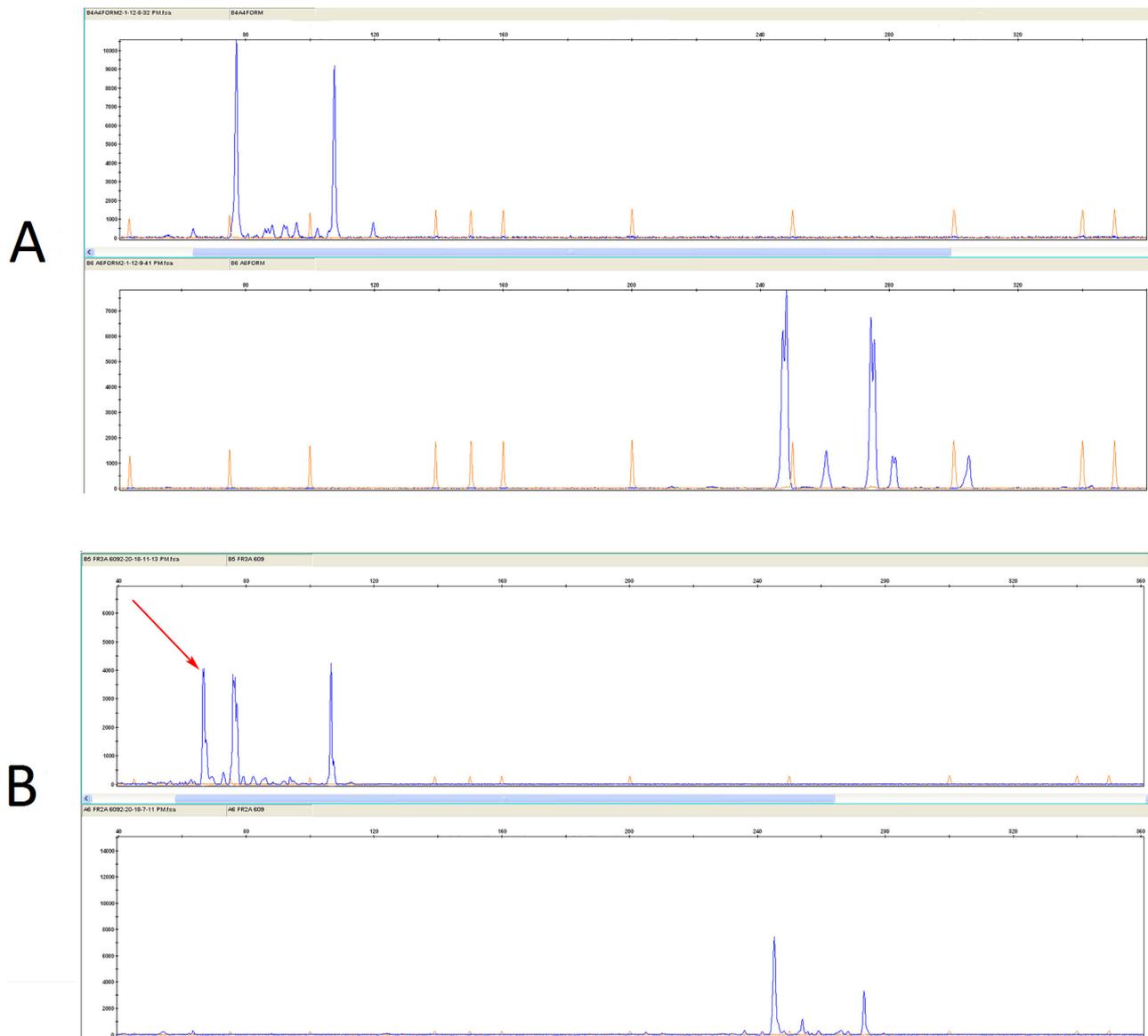
**Fig. 1.** Histologic and immunohistochemical feature of nodal marginal zone lymphoma. Hematoxylin and eosin stain, showing a nodular architecture on low power (A). The lymph node consisted of small to medium sized cells with scant or clear cytoplasm and with occasional admixed large cells (B). Collection of foamy histiocytes at the periphery of neoplastic nodule (C). Immunohistochemically staining: CD20 found primarily in a nodular pattern on low power (D), polymorphic neoplastic cells shown on high power (E), being also positive for MUM-1 (F).

## 2. Case presentation

A 63-year-old female presented with slow growing tumor mass in the left femoral region. Whole-body multi-slice computed tomography (MSCT) showed no abdominal or mediastinal lymphadenopathy and no splenomegaly. However, the patient had abnormal coagulation tests, i.e. prolonged activated partial thromboplastin time (APTT) and prothrombin time (PT). Factor VIII (FVIII) was elevated and serologic testing revealed the presence of highly elevated lupus anticoagulant (LA1/LA2 = 2.41). Other coagulation factors were normal or slightly elevated, and the patient was transferred to Rijeka University Hospital Centre for additional examination.

Additional imaging methods revealed another two iliac lymph

nodes, smaller than 0.7 cm in diameter. Surgical excision of the tumor mass, measuring 4 cm in greatest dimension, in femoral region was performed and histopathologic analysis revealed a lymph node with altered architecture. On low-power field microscopy, the lesion was characterized by nodular growth pattern of lymphatic cells surrounded by fibrous tissue with eosinophils, foamy histiocytes, adipocytes and mastocytes (Fig. 1A-C). Within the nodules, immunohistochemically, follicular dendritic cells were CD23+, while the nodules were filled with lymphocytes mostly of B phenotype (CD20+, PAX-5+) that were BCL-2+, MUM-1+, CD10-, BCL-6-, CD5-, CD15-, CD30- and cyclin D1-. The nodules were by far less filled with T lymphocytes (CD3+, CD5+, CD57-) (Fig. 1D-F). Majority of lymphocytes were polymorphic, mostly of medium size, with only few dispersed large cells, centroblast or

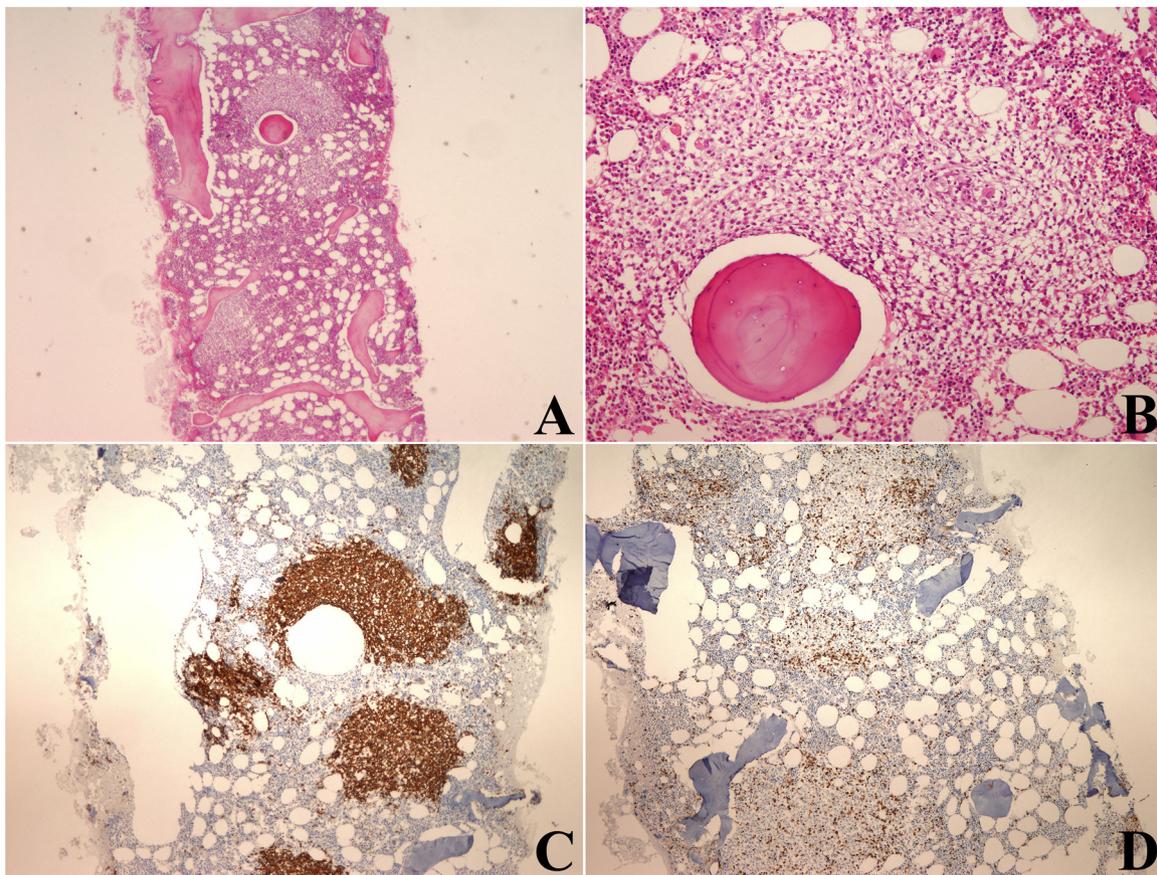


**Fig. 2.** GeneScanning of PCR products. PCR based immunoglobulin clonality testing was performed using FR2A and FR3A multiplex primers. (A) These two electropherograms show clonality testing of the initial NMZL sample using FR3A (top part of the figure A) and FR2A (bottom part of the figure A) multiplex primers. The top electropherogram shows two clonal peaks (the tallest blue peaks), one close to 80bp and second around 110bp (within expected range of the specific fragments produced by used primer sets). Those two clonal peaks confirm biallelic rearrangement within immunoglobulin receptor gene of the lymphatic population supporting the NHL diagnosis. The same thing is shown in the bottom part but using FR2A multiplex primers where two tallest blue peaks are around 250bp and 275bp (peaks are within expected range of the specific fragments produced by used primer sets) confirming mono-clonality of the tested lymphocyte population and supporting the NHL diagnosis. (B) These two electropherograms show clonality testing of the relapsing sample with DLBCL transformation using FR3A (top part of the figure B) and FR2A (bottom part of the figure B) multiplex primers. Subsequent GeneScan showed two clonal peaks (tallest blue peaks-biallelic rearrangement) in FR3A and FR2A multiplex PCR tubes but in the top part of the figure B (FR3A multiplex primers used) additional third peak appears (red arrow) suggesting further molecular genetic changes within the large B-cell population. However, it is not possible to exclude that the third peak indicates clonally unrelated large, blastoid transformed B-cell population, because we were not able to perform microdissection of large cell population with subsequent clonality analysis. All of the clonality analyses were performed in triplicates.

immunoblast. The Ki-67 proliferation index within the nodules was approximately 25%.

GeneScan PCR (polymerase chain reaction) clonality analysis of immunoglobulin (Ig) receptor showed two clonal peaks (biallelic rearrangement) confirming the clonal Ig rearrangement suggestive of B-cell lymphoproliferative disorder (Fig. 2) [12,13]. Thus, histologic, immunohistochemical and molecular analysis were very suggestive of the NHL diagnosis, a NMZL. Also, serology for Epstein-Barr virus, cytomegalovirus and parvovirus was negative for the active infection. Patient did not receive any treatment at this point. Eight months after the initial clinical presentation, the patient presented with enlarged

inguinal lymph node accompanied by night sweats and pain in the lower abdomen. Bone marrow biopsy showed hypercellular marrow with peritrabecular infiltrates of atypical neoplastic lymphatic cells and a reduced number of hematopoietic cells. Nodular infiltrates contained medium to large size atypical polymorphic lymphocytes with one or more nucleoli. Immunohistochemically, infiltrates were CD20+, CD79a+, CD5-, CD3- and made up more than 40% of the nuclear bone marrow cells (Fig. 3). Bone marrow biopsy findings corresponded to previously diagnosed lymphoproliferative malignancy (NHL, NMZL). Computed tomography (CT) revealed diffuse enlargement of abdominal and pelvic lymph nodes, as well as one axillary lymph node measuring



**Fig. 3.** Bone marrow biopsy involved with nodal marginal zone lymphoma. Peritrabecular infiltrate of small to medium size lymphocytes on low (A) and high power view (B); immunohistochemically positive for CD20 (C) and negative for CD5 (D).

up to 4 cm. Immunochemotherapy, according to the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) protocol was introduced. Disease remission was achieved after 8 cycles of R-CHOP, Control positron emission tomography-computed tomography (PET-CT) scans were normal and bone marrow biopsy showed normocellular intertrabecular spaces with no infiltrates of lymphoproliferative disease. Moreover, normalization of PT and APTT was observed.

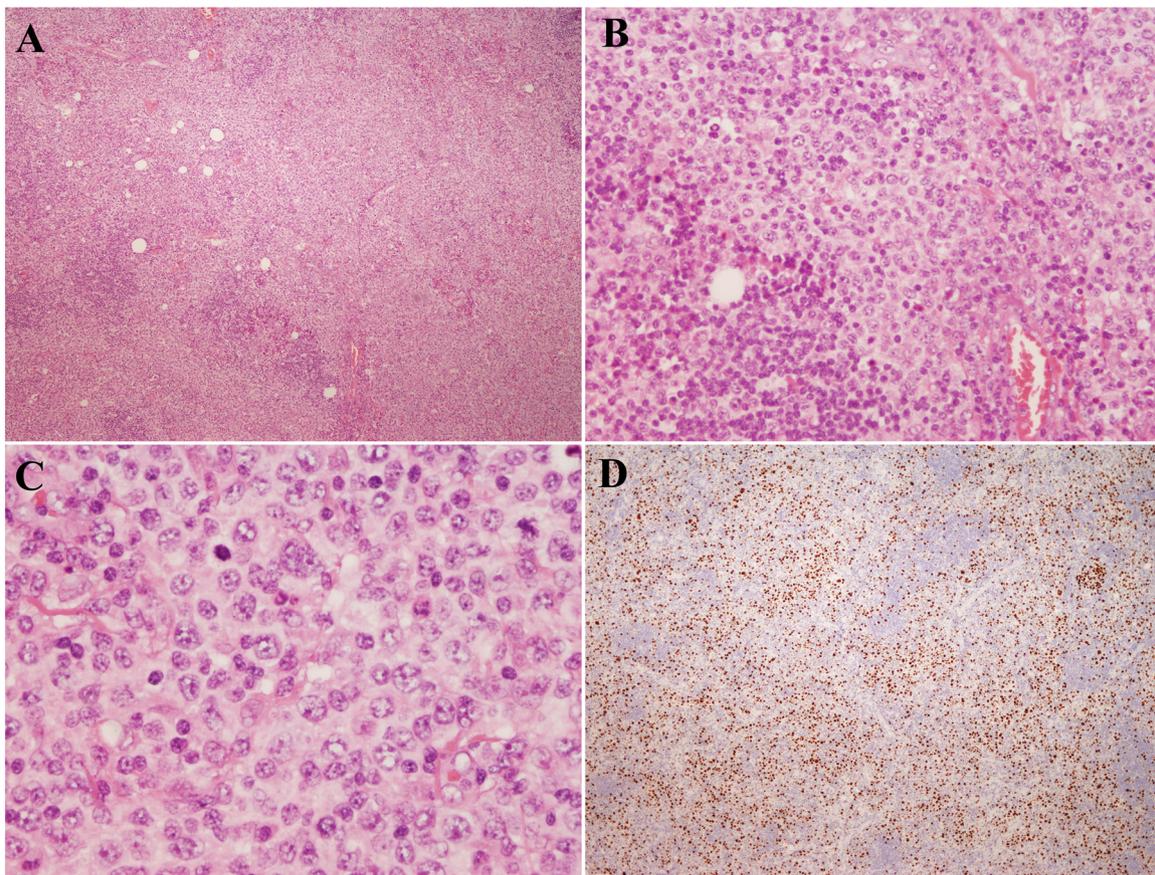
Forty seven months after the initial presentation, a growing mass (3.8 cm in greatest dimension) was noticed at the patient's back. Fine needle aspiration confirmed relapse of the lymphoproliferative disease. Following mass extirpation, histological examination, showed diffuse sheets of neoplastic cells, small to medium size atypical lymphocytes and great areas of large cells (Fig. 4). Lymphocytes were CD20+, CD79a+, CD3-, CD5-, CD43-, Bcl6-/+, CD10- and MUM-1+. Moreover, staining with CD21 demonstrated the presence of a dendritic cell network remnants. The Ki-67 proliferation index was increased (around 50%). These findings confirmed relapse of the NMZL, with focuses of transformation in DLBCL. Moreover, PET-CT showed significant morphological and metabolic progression of disease within subcutaneous nodular lesions at the back of thoracic and lumbar region, as well as in the outer layer of the paravertebral muscles (the largest lesion measuring 2 x 0.7 cm). Bone marrow biopsy showed no malignant infiltration, while PT and APTT were within the normal range. The patient underwent 6 cycles of the R-CEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisolone) chemotherapy protocol. Control PET-CT confirmed disease remission. Additional serologic tests (anti- $\beta$ 2-GPI IgM, anti- $\beta$ 2-GPI-IgG, aCL-IgG, aCL-IgM and LA) for suspected APS showed elevated anti- $\beta$ 2-GPI IgM titer (78.15 RU/mL; normal < 20 RU/mL). Antinuclear (ANA), extractable nuclear (ENA) and double-stranded DNA (dsDNA) antibodies were negative suggesting absence of

the possible underlying autoimmune disease.

### 3. Discussion

The present case report describes NMZL at the time of initial diagnosis and DLBCL in the relapse, with concurrent elevated LA and anti- $\beta$ 2-GPI IgM, respectively. It is well known that immune dysregulation following organ transplantation, infection, immunodeficiency states, and autoimmune diseases or syndromes, increases the risk of certain lymphomas. Moreover, the presence of aPL antibodies in lymphoma patients, either with simultaneous or non-simultaneous presentation, is well recognized [14]. Several possible explanations have been proposed, e.g., aPL antibodies may be due to malignant B lymphocytes or B-cells that are activated via cytokine secretion by malignant T-cells [15]. Or it is plausible that aPL antibodies may be produced by reactive B-cell population in the context of B-cell lymphoproliferative disorder (reviewer's comment). Moreover, a particular cancer immunotherapy (e.g., interferon alpha) may induce their production. The possibility that tumor cells directly synthesize antibodies has been well documented in case of multiple myeloma or Waldenström's macroglobulinemia [16]. In order to exclude lymphoplasmacytic lymphoma, we additionally performed MYD88 L256P mutation analysis, and our case was negative for the mentioned mutation.

According to many studies, the prevalence of aPL antibodies in patients with different types of lymphoproliferative disorders was relatively high, between 26.6%–41% [17–21]. However, pathogenicity of aPL antibodies in NHL is not very clear, they do not seem to correlate with thrombotic events or other manifestations of APS, though thrombotic events associated with aPL antibodies can be the first manifestation of malignancy including NHL [21]. Most literature reports confirm the association of aPL antibodies and B-cell lymphoma,



**Fig. 4.** Nodal marginal zone lymphoma with transformation to diffuse large B-cell lymphoma. High-grade component is consisted mainly of large cells that are arranged in sheets (A–B), primarily of centroblastic cytology (C), with high Ki67 proliferative activity (D).

however T lymphocyte lymphoma such as mycosis fungoides and angioimmunoblastic T-cell lymphoma combined with aPL antibodies have also been reported [22,23].

In our case, the patient had NMZL, an indolent NHL of B lymphocytes with aPL antibodies. To the best of our knowledge, only one case of marginal zone lymphoma within the splenic hilar lymph nodes associated with elevated serum antibodies against cardiolipin and splenic infarctions has been described in the literature [24]. On the other hand, the splenic variant of marginal zone lymphoma, according to literature data, is relatively frequently associated with immune mediated paraneoplastic phenomena such as autoimmune hemolytic anemia, autoimmune thrombocytopenia and C1 esterase inhibitor deficiency. A multicenter retrospective study including 70 patients with splenic marginal zone lymphoma, Gebhart et al. (2014) found LA in 13% of patients and these patients had a higher occurrence of venous thromboembolic events as compared with LA negative patients [25]. Moreover, none of the patients with LA had persistent complete remission of LA after splenectomy, but complete remission of LA was achieved after rituximab-bendamustine immunochemotherapy. Thus, the authors concluded that using immunochemotherapy may be considered as first line therapy in splenic marginal zone lymphoma patients with LA.

Although a relatively high overall prevalence of aPL antibodies was detected in NHL patients, thrombosis was very uncommon among these patients. Tincani A et al. reported that the presence of aPL antibodies in asymptomatic subjects can not cause thrombosis when a second factor is absent (the 'two hits hypothesis') [16]. Malignancies are considered as a possible 'second hit' that can trigger thrombotic events. In addition, patients with a solid malignancy are much more likely to have a thrombotic event compared to patients with hematologic disorders. So, even if high levels of aPL antibodies are more frequent in hematologic malignancies, clinical manifestations would be rarer [16]. In the study

by Genvesse et al., aPL antibodies were found in 26.6% of NHL patients and none of the patients developed a thromboembolic event [18]. Consequently, the authors concluded that vessel compression by lymphoma, but not elevated aPL antibodies, remains the main cause of thrombosis in NHL patients [18]. Our patient had no history of thrombosis. Initially, she developed LA, and in relapse, anti- $\beta$ 2-GPI antibodies. Human  $\beta$ 2-GPI is a plasma glycoprotein that can act as a physiologic anticoagulant inhibiting the clotting cascade and platelet aggregation. The antibodies are directed not only against phospholipids but also against a complex of a phospholipid with one of the phospholipid-binding plasma proteins (cofactors), such as  $\beta$ 2-GPI and prothrombin [26]. Our patient had NHL and anti- $\beta$ 2-GPI antibody positivity which showed higher correlation with thromboembolic complications. Systemic reviews have shown that LA is stronger risk factor than aCL and anti- $\beta$ 2-GPI antibody for both arterial and venous thrombosis and obstetric complications [27]. Several retrospective and prospective studies have shown that triple aPL positivity correlates more strongly with thrombosis and pregnancy related complications than the presence of single or double positivity [28,29]. Should asymptomatic aPL positive patients receive primary thromboprophylaxis is still a matter of debate. Some studies have shown that one may consider primary thromboprophylaxis only in triple aPL positive subjects or in those carrying underlying (autoimmune) disease [27].

Normalization of aPL antibodies after treatment with rituximab has been previously described. As reported elsewhere this could be of high importance since it may be related to future utilization of rituximab to treat APS, in particular catastrophic APS [30]. Disappearance of aPL antibodies related to chemo-radiotherapy supports the hypothesis that they are directly produced by clonal cells, or by the immune system as a normal response to the tumor antigens. Pusterla et al. reported that the antibodies disappear independently of the lymphoma response to

treatment; accordingly, the latter hypothesis seems even more plausible [17]. In the study by Sciarra et al., all patients that responded to treatment exhibited normalization of their aPL antibody titers, whereas elevated aPL antibody levels persisted in non-responders [31]. Aggressive rituximab treatment is also potentially curative in patients with catastrophic antiphospholipid antibody syndrome and pulmonary mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) and may dramatically decrease the mortality risk [32]. The use of R-CHOP has been shown to be effective in treating patients with aPL antibody positive large B-cell lymphoma [33,34]. In our case, at relapse, we diagnosed NMZL transformation in DLBCL, because sheets of large cells were present with concurrent increase of proliferation index as measured by Ki-67 immunohistochemistry. We also performed immunoglobulin heavy chain fragment length analysis of recurrent NMZL with large cell transformation which showed additional, third clonal peak suggesting, further molecular genetic changes within the large B cell population (Fig. 2). However, it is not possible to exclude that the third peak indicates clonally unrelated large, blastoid transformed B cells since we were not able to perform microdissection of large cell population with subsequent clonality analysis.

Since our patient has not only had NHL but also aPL antibodies, the question arises whether it influenced the prognosis. According to some authors, aPL antibodies are not a useful predictor of treatment outcome or overall prognosis [17]. Yet, a more recent study claims that aPL antibodies may play a role as a prognostic marker in NHL. In the study by Bairey et al, 41% of NHL patients had elevated aPL antibodies at diagnosis and a statistically significantly shorter 2-year survival compared to patients without aPL antibodies at diagnosis [35].

In the context of all previously said, it should be suggested that not all NHL patients need to be screened for aPL antibodies routinely, only those with coagulation tests abnormalities and thrombotic events. In asymptomatic aPL positive subjects treatment of the underlying B-cell NHL using rituximab usually leads to aPL antibody disappearance, however one should consider thromboprophylaxis in high risk patient groups (triple aPL positivity). Thus our recommendation for the treatment of patients with aPL antibodies and NMZL would be R-CHOP or R-bendamustin, which is very immunosuppressive therapy. After therapy completion we suggest clinical follow-up with periodic testing of the aPL antibodies level.

#### 4. Conclusion

In conclusion, we documented the coexistence of autoimmune reaction and underlying lymphoproliferative disorder, aPL antibodies and NMZL, respectively. The presence of aPL antibodies in NHL is frequent but it is not common in the NMZL. To the best of our knowledge, only one case of marginal zone lymphoma within the splenic hilar lymph nodes associated with elevated serum antibodies against cardiolipin and splenic infarctions has been described in the literature. We report a unique case of NMZL with transformation into DLBCL with concurrent aPL antibody positivity. The aim of present case report is to highlight the possible underlying increase of aPL antibodies in NMZL patients with coagulation tests abnormalities. This is of clinical importance because one should be aware of possible thrombotic complications and consider strict control or adequate thromboprophylaxis in high risk patient groups.

#### Conflict of interest

The Authors declare that there is no conflict of interest.

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#### Research ethics

All the clinical data obtained and tissue analyses results were handled with the care and respect to patient's anonymity and approved by Ethical Committees of the Rijeka University Hospital Centre and Faculty of Medicine, University of Rijeka.

#### Patient consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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