

Transformation of low-grade follicular lymphoma with partial marginal zone differentiation: Two cases

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Abstract

Two cases of low-grade follicular lymphoma, with marginal zone differentiation and/or with high proliferation rate in one of them, are reported with transformation into high grade B-cell and B-lymphoblastic lymphomas. The contribution of these features to the transforming process, although previously described, is infrequent, and has not been deciphered to date.

Introduction

Follicular lymphoma grade 1-2 is a low-grade B-cell lymphoma which classically follows an indolent course, but is mostly resistant to treatment for cure. Moreover, this malignant tumor shows a 40% overall propensity for a transformation into diffuse large B-cell lymphoma, classic Hodgkin lymphoma, acute lymphoblastic leukemia/lymphoma, as well as others. Recently, progression of this tumor to a high grade B-cell lymphoma has been reported.¹

Case Report #1

The patient, a 56-year-old male, underwent a left inguinal lymph node resection in November 2017. This was diagnosed as grade 1-2 follicular lymphoma. Some of the tumoral follicles were surrounded by a band of irregular cells with clear cytoplasm (Figures 1 and 2), which, in contrast to the follicles, that were staining strongly and diffusely positive for CD10, Bcl6 and Bcl2, showed only weak and partial positivity for CD10, weaker positivity for Bcl2 and was negative for Bcl6 (Fig 3-5). Therefore, marginal zone differentiation of the follicular lymphoma was considered.

Moreover, in the follicular centers, the proliferation fraction reached 50%, using

Ki-67 expression.

In January 2018, the patient was submitted to a left orchiectomy. Involvement of the testis and the spermatic cord by follicular lymphoma was identified. In this location, BCL-6 immunostaining was negative and Ki-67 expression (performed twice) was 1%.

In January 2019, a mass was palpated in the patient's right breast and tru-cut biopsies were carried out. The breast was infiltrated by atypical cells, mostly small- to medium-sized, with vesicular nuclei and unremarkable nucleoli. Immunophenotypic findings revealed CD20 (-); CD79a +++; CD10 +++; BCL-6 (-); BCL-2 +++; MUM1 +++; CD99 +++; TdT (-)/+ in 25% of tumor cells; C-MYC +++; Ki-67 + in 95% of tumor cells.

FISH for BCL-2, t(14;18) was evident in 82% of tumor cells, while FISH for C-MYC showed t(8;14) in 84% of cells.

FISH for MYC was performed retroactively from the initial inguinal lymph node and from the orchiectomy specimens, in order to exclude a pre-existing MYC rearrangement in the low-grade follicular lymphoma. However, three attempts at the FISH failed, due to lack of signals.²

The findings were interpreted as aggressive B-cell lymphoma. Our differential diagnosis included high grade B-cell lymphoma with MYC and BCL2 rearrangements, transformed from follicular lymphoma and, due to the partial positivity for TdT, B-lymphoblastic lymphoma, transformed from follicular lymphoma. According to the literature, TdT expression in such cases could cause a diagnostic dilemma.³ While, according to the "WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues", they should be classified as B-lymphoblastic leukemia/lymphoma, cases of TdT-positive high-grade B-cell lymphomas have been described.⁴

A bone marrow biopsy, obtained two days after the breast biopsy, showed interstitial infiltration by a tumor, similar to that, seen in the breast. The bone marrow aspiration demonstrated abundant blastoid cells, comprising 95% of all nucleated population. The flow cytometry analysis of the bone marrow identified a large population of B-lineage cells with a low-moderate right-angle light scatter and variable, from low to moderate strong positive expression of CD45. Gated pathological cells were positive for surface CD10, CD19, CD24, CD38, CD43, CD58 and HLA DR and positive for intracellular CD79a. They showed a low expression of CD22 and were negative for surface CD5, CD20, CD23, CD34, CD79b and surface IgM. They were nega-

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tive for immunoglobulin light chains by cytoplasmic staining, but showed a clear positive staining for cytoplasmic IgM heavy chains. The findings were interpreted as suggestive for B-lymphoblastic lymphoma/leukemia, most probably of pre-B phenotype, with the possibility of diffuse large B-cell lymphoma as a less probable diagnosis.

Due to the core biopsy, aspiration and flow cytometry results, in the patient's clinical setting, the diagnosis of for B-lymphoblastic lymphoma/leukemia was preferred by the hematologists.

The patient was started on R-CHOP and on IT treatment with ARAC+MTX+Dexamethasone. PET-CT, after 4 cycles of treatment pointed at a partial

response with hypermetabolic cervical, axial and inguinal lymphadenopathy.

We switched therapy to Bendamustin-Gazyva, HD MTX. PET-CT, after 3 cycles of the 2nd line treatment showed a very good response and this treatment was therefore pursued. Two weeks later the patient was readmitted to the hospital in a confusional state and with vomiting. An MRI of the brain showed parenchymal involvement and an LP examination displayed leptomeningeal spread. Intensive IT therapy with MTA + ARA-C was initiated, without improvement. PET-CT showed diffuse bone involvement with high FDG uptake. Repeated bone marrow biopsy showed progression to B-cell lymphoblastic leukemia. Three weeks later the patient died.

Case Report #2

This patient was a 68 years-old male, with a clinical history of follicular lymphoma grade 1-2, stage IV, first diagnosed

in 2004, treated with R-CHOP and CVP with partial remission. The patient had been very partially monitored.

In 2020 he was examined due to back pain, weakness and sleep disturbances, but no B-symptoms. Hematological and biochemical studies showed leukocytosis, WBC $15.9 \times 10^9/L$ and LDH 13.765 U/L. Excisional biopsy of a left inguinal lymph node and bone marrow biopsy was performed.

The lymph node architecture was effaced by a lymphoid infiltrate, showing vague nodularity and composed of small irregular cells, the centroblastic count was about 6. No evidence of polarization, tingible body macrophages, nor mantle zones, were identified. Around some of the nodules, bands of cells with clear cytoplasm were noted (Figure 6). Extracapsular extension and infiltration of small blood vessels' walls were present. The neoplastic follicles stained positive for CD20, CD10 and Bcl2 and were negative for Bcl6. C-MYC was positive in isolated cells only. Intrafollicular cells showed Ki67 of about 25-30%.

The bone marrow was hypercellular for age, showing a widespread dense interstitial lymphoid infiltrate, composed of small to medium cells with large nuclei displaying finely dispersed chromatin and with scant cytoplasm (Figure 7).

In the bone marrow infiltrate CD20 stained with variable intensity: mostly

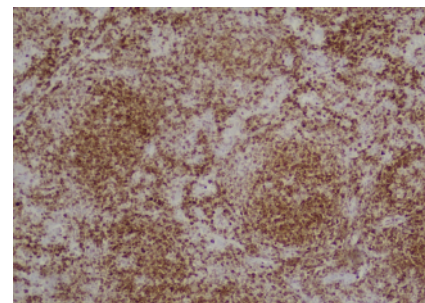


Figure 5. Follicular lymphoma with marginal zone differentiation, case 1, immunostaining for Bcl2. The tumor follicles stain strongly and diffusely positive for Bcl2, with the clear cell bands showing weaker staining (Bcl2, x100)

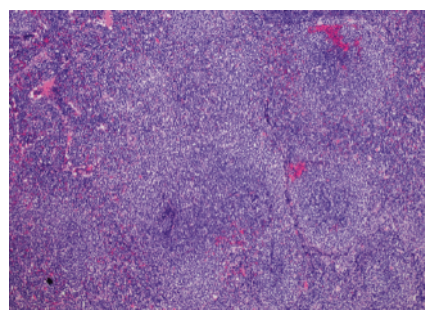


Figure 1. Follicular lymphoma with marginal zone differentiation, case 1. The tumor follicles are surrounded by a zone of cells with clear cytoplasm (H&E, x100).

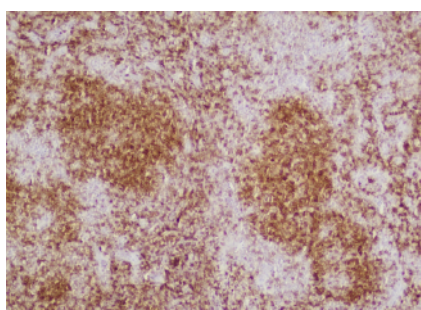


Figure 3. Follicular lymphoma with marginal zone differentiation, case 1, immunostaining for CD10. The tumor follicles stain strongly and diffusely positive for CD10, with the clear cell bands showing only weak and partial staining (CD10, x100).

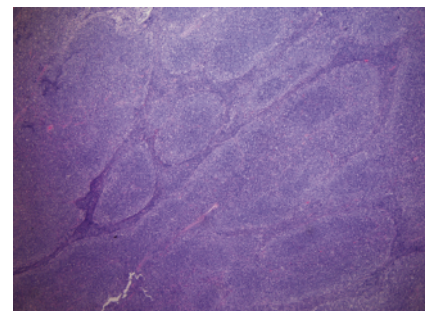


Figure 6. Follicular lymphoma with marginal zone differentiation, case 2. The tumor follicles are back-to-back, poorly circumscribed and surrounded by a band of marginal zone differentiation (H&E, x100).

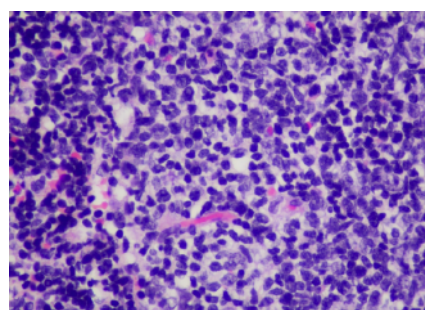


Figure 2. Follicular lymphoma with marginal zone differentiation, case 1, high power view. The zone of irregular cells with clear cytoplasm is in the middle third of the figure with the tumor follicle in the right third. (H&E, x400).

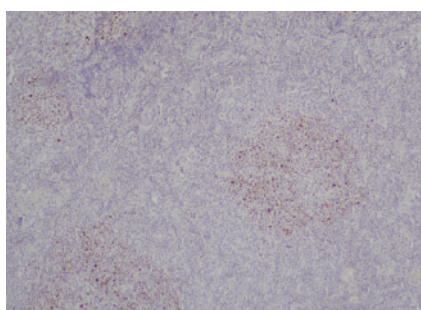


Figure 4. Follicular lymphoma with marginal zone differentiation, case 1, immunostaining for Bcl6. The tumor follicles stain positive for Bcl6, the marginal zones are negative (Bcl6, x100).

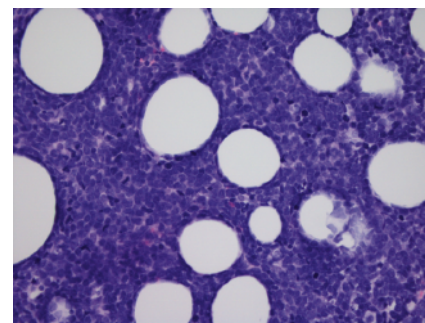


Figure 7. Bone marrow infiltration by high grade B-cell lymphoma with BCL-2 and C-MYC rearrangements, case 2. The tumor is represented by small to medium cells with high nucleocytoplasmic ratio and blastoid phenotype (H&E, x400).

weak, also negative or strong. CD10 was strongly and diffusely positive, Bcl6 was weakly positive in about 50% of the cells. The infiltrate was also positive for MUM1 and Bcl2 (focal) and negative for TdT. C-myc was positive in 95-98% of the cells, Ki67 proliferation index was as high as 100%.

Molecular biology studies

FISH for C-myc and BCL2 were performed. t(8;14) was identified in 81% and t(14;18) in 89%, therefore confirming the diagnosis of high-grade B-cell lymphoma with BCL-2 and C-MYC rearrangements, originating from a follicular lymphoma.

A treatment with R-CHOP was started. Two weeks after discharge the patient was readmitted to the hospital due to significant deterioration of his general condition, attributed to the progression of his lymphoproliferative disease and signs of tumor lysis syndrome. The patient was treated by hydration and Rasburicase with rapid laboratory improvement. A second line protocol with GEMOX was initiated, but without benefit.

Due to additional neurological symptoms, the patient underwent a lumbar puncture. Six pathological cells on flow cytometry, were consistent with CNS involvement.

The ICE protocol was applied together with intrathecal therapy with MTX + ARAC.

Under this therapeutic modality, the patient developed a significant decrease in all blood counts with marked neutropenia, severe electrolyte imbalance, high fever with pneumonia.

On March 13, 2020 death was ascertained.

Discussion

In the clinical setting of known follicular lymphomas, the most frequent subtype of histological transformation is into diffuse large B-cell lymphoma. In this report we describe two unusual variants of the tumor progression. One of them was preceded by a low-grade FL with marginal zone differentiation.⁴ The other was consistent with a low-grade FL with a high proliferation rate.⁵ These subsets of low-grade lymphomas exhibit a conduct that is inappropriate for the histopathologic description. Aggressive tumors, identified in bone marrow and breast biopsies of case 1, are classified according to the “WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues” (2017),⁴ as high-

grade B-cell lymphoma with BCL-2 and C-MYC rearrangements, originating from a follicular lymphoma. However, according to the same source, this term should not be used for the progression of low-grade follicular lymphoma into aggressive tumors, demonstrating the phenotype of B-lymphoblastic leukemia, as it was seen in the case 1. Such cases should rather be classified as lymphoblastic transformation of a follicular lymphoma.¹ The MYC rearrangement has been described also in this rare form of transformation, concomitant with a BCL2 translocation.

Foci of marginal zone differentiation have been described in about 10% of follicular lymphomas.⁴ Follicular lymphoma with marginal zone differentiation, according to some authors,^{7,8} is defined as a high-risk variant with significantly shorter survival than pure FL. Such a behavior may possibly be explained by multiple additional genetic aberrations, identified in this variant.⁹ In addition, the first case showed a high proliferation index in the primary low-grade tumor (>40%), which is itself associated with more aggressive course, comparable to grade 3 FL.¹⁰

Conclusions

This report concerns two infrequent modes of transformation of follicular lymphoma: lymphoblastic and a change of low-grade follicular lymphoma into high grade B-cell lymphoma with BCL-2 and C-MYC rearrangements. This later entity was previously described as “B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma”. The term double hit or triple hit configuration is also used depending on evidence of two or three translocations of the genes C-MYC, BCL-2 and/or BCL-6.^{4,9}

Both cases presented a preliminary marginal zone differentiation, while case 1 displayed in addition a high proliferation rate in the neoplastic follicles. The aggressive B-cell lymphomas were characterized in both cases by the similar clinical course: aggressive behavior with bone marrow and CNS involvement and lack of response to chemotherapy.

These findings probably support the role of marginal zone differentiation as a high-risk factor in the clinical setting of low-grade follicular lymphoma and may be suggestive of its association with subsequent development of unusual variants of histologic transformation. In addition, in the

context of multiple additional genetic aberrations, previously described in this variant of follicular lymphoma, the presence of alternative transformation pathways of follicular lymphoma may be postulated.

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