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CASE REPORT

Follicular lymphoma (in situ) pattern in the bone marrow: does it indicate an early stage in disease evolution?

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Key Clinical Message

Bone marrow involvement by an isolated interstitial lymphoid aggregate exhibiting the pattern and phenotype described for follicular lymphoma in situ (FLIS) has not been reported before. The detection of clinically silent FL in this case highlights the necessity of complete staging workup when such lesions are encountered in biopsies.

Keywords

BCL2, bone marrow, CD10, follicular colonization, follicular lymphoma, in situ.

A 66-year-old, otherwise asymptomatic, man presented to our institution for follow-up evaluation of nonprogressive, normocytic anemia, and mild thrombocytopenia discovered a year ago (hemoglobin = 12.7 g/dL, platelets = 134,000/μL). The WBC count was normal. Physical examination revealed a 1 cm right axillary lymph node and a spleen tip was felt on inspiration. Ultrasonography revealed mild splenomegaly with hypo echoic lesions.

Due to a suspicion of lymphoma, flow cytometric analysis of the peripheral blood was performed, which did not detect any T- or B-cell abnormality or any light chain-restricted B-cell population. Serum protein electrophoresis and immunofixation analyses did not detect any monoclonal paraprotein.

The bone marrow biopsy, however, revealed a solitary, interstitial lymphoid aggregate, comprised predominantly of a core of centrocytic cells surrounded by a cuff of small lymphocytes (Fig. 1A and B). Immunohistochemistry showed the aggregate to be composed of CD20+ PAX5+ B-cells exhibiting intense CD10 and BCL2 expression (Fig. 1C and D), with CD3+ T-cells present at the periphery. No paratrabecular lymphoid aggregates were seen. Elsewhere, only rare, scattered small-sized B-cells were seen in the marrow interstitium and normal maturing trilineage hematopoiesis was evident. No distinct lymphoid aggregates or significant lymphocytosis was observed on morphologic evaluation of the bone marrow aspirate. Flow cytometry of the bone marrow aspirate was normal and conventional cytogenetic (G-band) analysis showed a normal male karyotype. FISH analysis using the *IGH-BCL2* dual color fusion probe did not detect *IGH/BCL2* rearrangement or copy number increase in chromosome 14q and 18q. PCR analysis of the peripheral blood and bone marrow aspirate samples for *IGH* gene rearrangement did not detect clonal products, confirming limited marrow involvement by the atypical B-cells, possibly also explaining the failure to detect BCL2 rearrangement. Since the bone marrow biopsy had undergone acid decalcification and the solitary lymphoid aggregate (described above) was not present on deeper levels, FISH and PCR analyses after microdissection of the aggregate could not be performed.

Marrow infiltration by follicular lymphoma (FL) is typically paratrabecular. However, a predominant or exclusive interstitial pattern of marrow involvement may be seen rarely and at times the lymphoid aggregates can

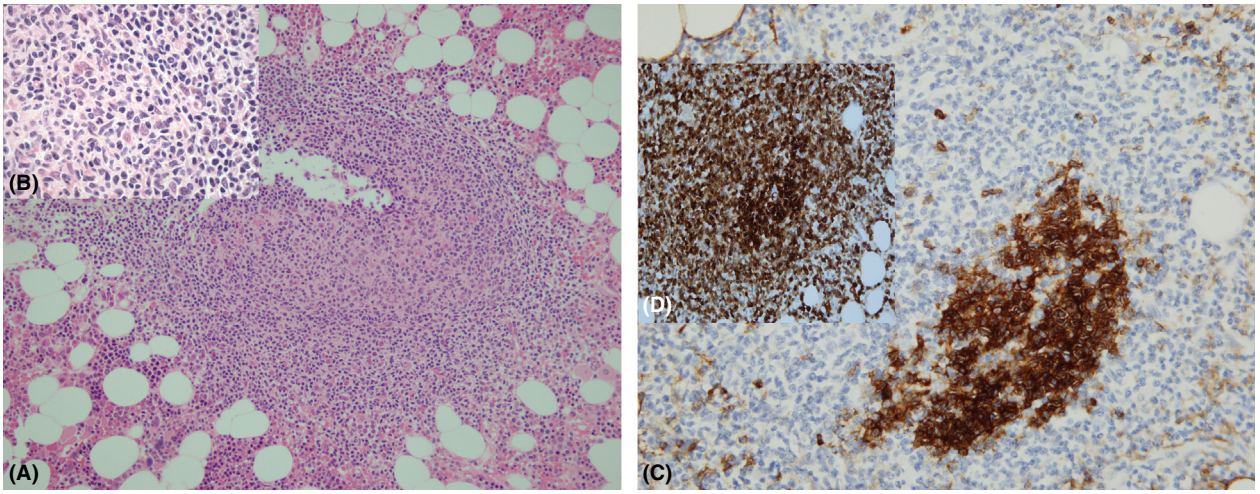

Figure 1. A solitary lymphoid aggregate in the bone marrow (A) showing a dense core of centrocytic cells (B), which exhibits intense CD10 (C) and BCL2 (D) expression. The surrounding cuff of lymphocytes was predominantly comprised of T-cells.

manifest cytoarchitectural features of neoplastic lymphoid follicles similar to those observed in lymph nodes involved by FL. The presence of an isolated interstitial lymphoid aggregate comprising bright CD10+ and BCL2+ B-cells has not been reported before in the bone marrow. The cytomorphology and phenotype of the neoplastic lymphoid aggregate is reminiscent of the pattern and phenotype described in lymph nodes (and occasionally extramedullary sites) involved by putative precursors of FL, which has been referred to as FL in situ (FLIS) [1].

At the time of bone marrow biopsy, it was unclear if the marrow finding reflected infiltration by low-level circulating clonal/neoplastic follicular B-cells at an early stage of FL evolution or limited marrow involvement by clinically silent FL. Given the bone marrow findings, a more thorough assessment for underlying FL was recommended. A PET-CT scan revealed PET-avid splenic lesions, retroperitoneal lymph nodes, and a focal lesion in the left rib. A spleen biopsy performed at another institution revealed low grade FL (grade 1-2/3). The patient was treated with rituximab and lenalidomide and reportedly had a complete clinical response.

In this case, bright coexpression of CD10 and BCL2 by B-cells colonizing the lymphoid aggregate could represent an early event in the homing or trafficking of FL to the bone marrow, as has been suggested before [2]. However, in the absence of molecular analysis it cannot be ruled out that the lymphoid aggregate temporally predated the development of FL at other sites. Nonetheless, this case highlights the necessity of a complete staging workup to detect clinically silent FL and to better understand the natural history of FLIS. Molecular analysis of additional such cases in conjunction with detailed clinical evaluation would be helpful in this regard. These studies could also help clarify whether or not the described pattern of marrow involvement by FLIS constitutes stage IV disease, as is the case for patients displaying the usual pattern(s) of marrow involvement by established FL at other sites.

Conflict of Interest

The authors have nothing to disclose.

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