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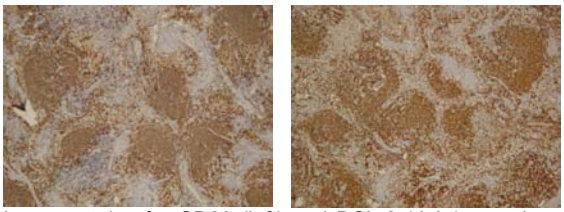
Focus on Immunohistochemistry - July 2001

BCL-2

BCL-2 is a commonly used immunohistochemical marker, and it has utility in the classification of lymphoid processes, recognition of certain epithelial tumors, and also some mesenchymal neoplasms.

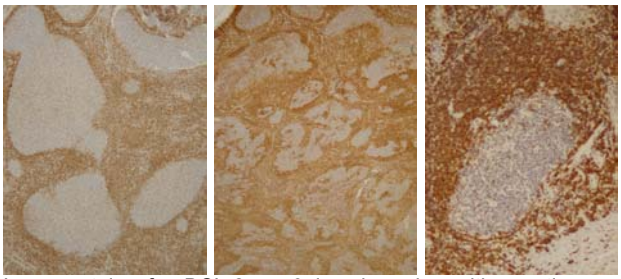
BCL-2 expression in primary ("resting") follicles: a potential diagnostic pitfall

Undoubtedly, BCL-2 is most commonly employed in the diagnosis of lymphoma, where it has particular utility in assisting in the distinction of reactive follicular hyperplasia vs. follicular lymphoma. It is very important to realize however, that BCL-2 is normally expressed in a large number of non-neoplastic B-cells and also non-neoplastic T-cells, so the fact that a certain lymphoid cell population expresses BCL-2 certainly does not mean that it is neoplastic. One cell population that normally expresses BCL-2 is the B-cells that are present within primary (or "resting") follicles, and it is only the germinal center area of a secondary ("activated") follicle that normally lacks



Immunostains for CD20 (left) and BCL-2 (right) on a lymph node referred for immunophenotyping. The nodular structures are benign primary (resting) follicles, which were CD10 negative and had a very low Ki-67 proliferative fraction.

significant expression of this marker. This is very important, since I suspect some pathologists may equate nodules of B-cells expressing BCL-2 with follicular lymphoma. However, if one is evaluating a lymph node containing a number of primary (resting) follicles (that do not possess germinal centers), a misdiagnosis of follicular lymphoma will be readily made if operating under that assumption, since the nodular collections of B-cells express BCL-2 in a lymph node containing resting follicles. CD10 (CALLA) and Ki-67 are useful in sorting out this problem, since resting follicles are negative for CD10 (CALLA) and have a very low Ki-67 (MIB-1) proliferative fraction. The cells of grade 1 follicular lymphoma are CD10 (CALLA) positive, and have a low to intermediate proliferative fraction, whereas the cells of a reactive germinal center are CD10 (CALLA) positive and have a very high Ki-67 (MIB-1) proliferative fraction. (In general, the proliferative fraction in follicular lymphomas increases with increasing numbers of large cells within the neoplastic follicles.)

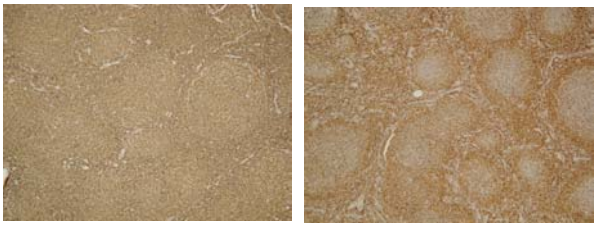


Immunostains for BCL-2 on 3 lymph nodes with reactive follicular hyperplasia. The reactive follicles are negative for BCL-2. The follicles in the middle photograph are quite irregular.

BCL-2 expression in follicular lymphoma

It is well known that follicular lymphoma frequently expresses BCL-2, unlike the germinal centers of secondary (activated) follicles. The frequency of expression of BCL-2 in follicular lymphoma varies with the type of follicular lymphoma. Expression of BCL-2 is present in nearly all cases of grade 1 follicular lymphoma (follicular small cleaved lymphoma), decreases to about 85% in cases of grade 2 follicular lymphoma (follicular mixed small and large cell lymphoma), and drops to about 75% in cases of follicular grade 3 lymphoma (follicular large cell lymphoma). The expression of BCL-2 within neoplastic follicles may be weaker than expression of this marker in the interfollicular lymphocytes, so at

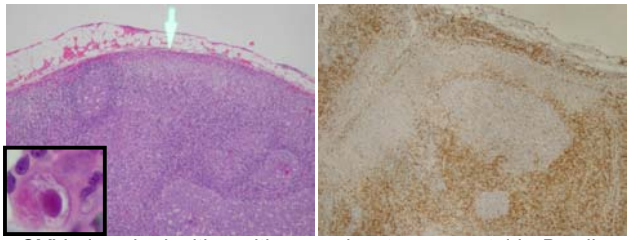
first glance on low-power, one might get the impression that the follicular structures are negative, whereas in fact they are expressing the marker but in a weaker fashion. It is very helpful to have a section of normal tonsil or reactive lymph node in your positive control material (which ideally should consist of some type of multitumor block preparation), to allow ready comparison of results on a particular case with a known reactive process. As noted above, expression of BCL-2 is certainly not specific at all for follicular lymphoma, and this marker is expressed in many normal B-cells and T-cells, other types of B-cell lymphoma (overall about 83% of cases), T-cell lymphoma (overall about 45% of cases), certain carcinomas, and some mesenchymal neoplasms.



BCL-2 expression in a grade 1 follicular lymphoma (left) and a grade 2 follicular lymphoma (right). Note that the expression in the grade 2 lymphoma is weaker than the surrounding interfollicular cells, but this should still be regarded as positive. The neoplastic follicles in both of these cases were CD10 positive with low to intermediate Ki-67 proliferative fractions.

BCL-2 expression in monocytoid B-cell proliferations, Burkitt and Burkitt-like tumors, and nodular lymphocyte predominance Hodgkin's

Expression of BCL-2 may also assist in the evaluation of lymphoid some proliferations that contain prominent collections of monocytoid B-cells. BCL-2 is negative in the monocytoid B-cells in reactive processes (such as that seen in cases of lymph nodes with toxoplasmosis), but up to 79% of cases of marginal zone B-cell lymphoma are positive with BCL-2. Therefore, expression of BCL-2 by a population of monocytoid B-cells should heighten the suspicion that it represents a neoplastic proliferation. In addition, BCL-2 may assist in the separation of Burkitt's lymphoma (which is BCL-2 negative) from Burkitt-like lymphoma (which is reported to be positive with BCL-2 in 67% of cases). Finally, the neoplastic B-cells of nodular lymphocyte predominance Hodgkin's disease are characteristically negative for BCL-2.



CMV lymphadenitis with prominent monocytoid B-cell clusters in the subcapsular sinus (left, arrow). CMV inclusions were identified on some cells in the lymph node (inset, left). Note that the subcapsular reactive monocytoid B-cells are negative for BCL-2 (right)

BCL-2 in the epithelial tumors

Dr. Battifora and colleagues published a paper in 1996 that studied the use of BCL-2 to aid in the distinction of breast carcinoma (79% positive) from lung carcinoma (5.6% positive) and gastric carcinoma (8.3% positive). In addition, there were also significant differences in the intensity of staining with this marker. 70% of the breast carcinomas were moderately to intensely positive, whereas only 1.9% of the lung carcinomas and only 0.9% of the gastric carcinomas showed moderate to intense reactivity for BCL-2. I have also seen BCL-2 positivity in female genital tract tumors, thyroid tumors, neuroendocrine tumors, and melanomas. In lung carcinoma, some authors have noted an association of BCL-2 positivity with neuroendocrine differentiation, in that most small cell carcinomas appear to be BCL-2 positive. BCL-2 may also have a role in helping to separate basal cell carcinoma of the skin (BCL-2 positive) from squamous tumors (BCL-2 negative), although in my experience Ber-EP4 performs better for this purpose.

BCL-2 in evaluation of mesenchymal neoplasms

BCL-2 is commonly expressed by certain types of mesenchymal tumors. Synovial sarcoma is positive in 80% or more of cases, and BCL-2 positivity is also expressed in the large majority of gastrointestinal stromal tumors (GIST). Other mesenchymal neoplasms that characteristically express BCL-2 include solitary fibrous tumor, spindle cell lipoma, Kaposi's sarcoma, giant cell angiofibroma, dendritic fibromyxolipoma, and most cases of lymphangio-leiomyomatosis. In contrast, leiomyosarcomas are characteristically BCL-2 negative. About one-third of cases of malignant peripheral nerve sheath tumor have been reported to express BCL-2.

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