

# Letters to the Editor

**CORRESPONDENCE RE: AGUILERA NS, TOMASZEWSKI MM, MOAD JC, BAUER FA, TAUBENBERGER JK, ABBONDANZO SL. CUTANEOUS FOLLICLE CENTER LYMPHOMA: A CLINICOPATHOLOGIC STUDY OF 19 CASES. MOD PATHOL. 2001;14:828–35. AND FRANCO R, FERNANDEZ-VAZQUEZ A, MOLLEJO M, CRUZ MA, CAMACHO FI, GARCIA JF, NAVARRETE M, PIRIS MA. CUTANEOUS PRESENTATION OF FOLLICULAR LYMPHOMAS. MOD PATHOL. 2001;14:913–9.**

**To the Editor:** We read with great interest the articles by Aguilera *et al.* (1) and Franco *et al.* (2), respectively. Aguilera *et al.* reported that primary cutaneous follicular lymphoma (PCFL) cases frequently expressed bcl-2 (11/18 cases), bcl-6 (15/15), and CD10 (14/17). Franco *et al.* described that all four cases of stage IV follicular lymphoma, diagnosed in skin biopsy, showed expression of CD10, bcl-6, and bcl-2 in the skin lesions. Additionally, they stated that 10 control cases of PCFL showed similar frequencies of expression of these markers.

We recently have finished a similar study in evaluating the expression of the above markers in PCFL and secondary cutaneous follicular lymphoma (SCFL), secondary cutaneous involvement by follicular lymphomas. We evaluated 11 lesions from nine patients with SCFL and four lesions from four patients with PCFL by immunohistochemistry on paraffin-embedded tissue (please refer to Table 1 for the staining method). The positive expression of these markers was defined as previously reported (3), briefly: 1) strongly positive (recognizable at low power, 20×) or moderately positive (recognizable at intermediate power, 100×, but not low power) staining intensity regardless of percentages of positive cells; or 2) weakly positive (only recognizable at 400×) staining intensity with more than 20% of cells being positive. Our results showed that the frequency of CD10, bcl-2, and bcl-6 expression in SCFL was 82%, 82%, and 56%, respectively. Additionally, SCFL expressed CD10 and bcl-2 more frequently than PCFL (82% vs. 25% for both markers,  $P < 0.05$ ,  $\chi^2$ ). The expression of bcl-6 appeared more frequent in SCFL than in PCFL but not statistically

significant (56% vs. 0%,  $P < 0.1$ ,  $\chi^2$ ). Six of nine cases with SCFL presented with stage IV disease. In contrast, all four cases of PCFL presented with stage I disease.

Consistent with the study by Franco *et al.*, our findings indicate that expression of CD10, bcl-2, and bcl-6 is frequent in SCFL. Additionally, the frequency of CD10, bcl-2, and bcl-6 expression in SCFL is compatible with that of follicular lymphoma at noncutaneous sites reported in literature. However, our results, in agreement with the report by the European Organization for Research and Treatment of Cancer (EORTC) (4), suggest that differences in CD10, bcl-2, and bcl-6 expression between SCFL and PCFL are substantial and may contribute toward the recognition of these two entities. This finding is different from that of the above two studies. The cause of the difference is uncertain. We speculate that this discrepancy may be explained, at least partially, by the different definition of staining positivity, different sampling of patients, and/or the different method in performing the immunohistochemical stains.

We suggest that further studies with a larger sample size and a standardized method be performed to clarify the issue on the expression of these markers in PCFL and SCFL. The distinction between the two entities has important therapeutic and prognostic implications as shown by the clinical presentation of our patients and the patients reported by Franco *et al.* and Aguilera *et al.*

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**TABLE 1. Characteristics of the Antibodies Used\***

Antibody	Clone	Manufacturer	Dilution
Bcl-6	NA+	Santa Cruz Biotechnology, Santa Cruz, CA	1:300
Bcl-2	124	Dako, Carpinteria, CA	1:100
CD10	56C6	Novocastra, Newcastle, UK	1:50

\* The method for epitope retrieval was a heating water bath at 100 °C with PH 6.0 citrate buffer for 35 minutes for all antibodies.

+ Not applicable, polyclonal.

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**In reply:** We have read with interest the article by Aguilera *et al.* (1) and the letter by Chang and coworkers (2). The comparison of the data of both papers with those reported by our group in two recent reports (3, 4) clearly indicates the lack of reproducible morphological criteria for the definition of the different types of cutaneous B-cell lymphomas (CBCL), which at the same time emphasizes the need for additional molecular or immunohistochemical markers for the recognition of these subtypes of CBCL. Thus, it seems that in the diagnosis of cutaneous follicular lymphoma (CFL), the used criteria differ from those standardized for its nodal counterpart. For the necessary clarification of the characteristics of these cutaneous lymphomas, we prefer to restrict the diagnosis of primary CFL to those cases showing a predominant follicular pattern (nodules of B-lymphocytes occupying lymphoid follicles as recognized by the presence of follicular dendritic cells) and germinal center cytology (centroblasts and centrocytes). When defined on this basis, all cases show bcl-6 expression, as their nodal counterparts, and the majority of them are also CD10+, which is confirmed by the findings of Aguilera *et al.* (1). Thus, it seems that germinal center cells, either in the skin or in the lymph node, benign or malignant, consistently tend to express bcl-6 and CD10, and to be situated within a network of follicular dendritic cells. The only relevant difference would be the overexpression of bcl-2 by tumoral GC cells, which seems to be at least partially independent of the presence of t14;18. Our data only show a potentially different marker between primary CFL and secondary FL, the presence of t14;18.

In the meantime, and until other, more characteristic molecular markers are provided, we

propose to use this conservative approach, which should permit the comparison of different series of patients.

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**In reply:** We read Chang *et al.*'s letter regarding our manuscript (Aguilera *et al.*, *Mod Pathol* 2001;14: 828–35) with interest. In that study, Chang and colleagues compared a limited number (4) of primary cutaneous follicular lymphomas (CFL) with 11 cases of secondary CFL. In our study, however, we attempted to study primary CFL only. We are therefore restricting the following comments to that aspect of Chang *et al.*'s inquiry.

The frequencies of bcl-6, bcl-2, and CD10 in our study appear to be much higher than in Chang *et al.*'s study, although they are comparable with three recent reports that study primary CFL. De Leval *et al.* (3) and Franco *et al.* (1, 2) reported bcl-6 in 7/7 (100%) and 15/15 (100%), bcl-2 in 6/7 (86%) and 9/15 (60%), and CD10 in 4/7 (57%) and 13/15 (86%) primary CFLs, respectively. Our study shows the best concordance with Franco *et al.* Cases used as primary CFL controls in Franco *et al.* (2) were reported in the larger study, Franco *et al.* (1), to which we refer above. We feel our findings, as well as those of De Leval and Franco, show a higher percentage of CD10, bcl-2, and bcl-6 than the 25%, 25%, and 0%, respectively, that Chang *et al.* reported in primary CFL, and that these markers may be diagnostically important. A greater number of

primary CFL and secondary CFL should be studied to confirm our results. We also agree that the significant differences in bcl-2 and CD10 expression that Chang *et al.* report in secondary CFL and primary CFL warrant further investigation.

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## Book Review

**Crowson AN, Magro CM, MC Mihm, Jr.: *The Melanocytic Proliferations. A Comprehensive Textbook of Pigmented Lesions, 560 pp, New York, Wiley-Liss, 2001 (\$299.00).***

The diagnosis of melanocytic neoplasms is one of the most difficult and controversial areas in dermatopathology. In recent years several books have been published on the subject, but only a few of them have made any significant contribution toward easing this task for the practicing pathologist and dermatopathologist.

The book written by Crowson, Magro, and Mihm is presented as a comprehensive review of pigmented lesions of the skin, encompassing the biology, diagnosis, and treatment of different melanocytic proliferations.

The book has a nice presentation and is well written and entertaining. It is fully illustrated with color photographs, which is a must. Most of the photographic material is of a very good quality; however, there are a few pictures that need improvement.

The book is divided into 15 chapters that cover all pigmented lesions of the skin, from freckles and lentiginos to the different types of nevi and malignant melanoma. Most of the chapters contain relevant clinical and therapeutic

information. Some of the chapters also include nonmelanocytic lesions in the differential diagnosis, with a reasonably good discussion. There are separate chapters devoted to immunohistochemistry, molecular and ultrastructural studies, and the biology of melanoma.

One of the drawbacks of this book is the splitting, categorizing, and subcategorizing of many lesions. This causes confusion, especially for the neophyte.

The book is uneven. For example, the Spitz's nevus chapter is an excellent and in-depth review of the subject. On the other hand, the chapter on dysplastic nevus is rather lengthy and does not simplify the issue; on the contrary, it creates more confusion. The discussion of melanoma also could be simplified. Obviously the authors have reviewed all the relevant literature about the subject, but not all of what has been written on melanomas is accurate or useful.

Despite the problems noted in this book, it will be a valuable reference for pathologists, dermatopathologists, and dermatologists.

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