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Review

In situ follicular neoplasia

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Abstract

This CARD addresses the following questions: 1) how should in situ follicular neoplasia be defined and diagnosed? and 2) how should people/patients with in situ follicular neoplasia be managed?

Keywords
In situ follicular neoplasia; intrafollicular neoplasia; early lesions in lymphoid neoplasia

Identity

The term in situ follicular neoplasia has been adopted very recently to classify a B-cell lymphoid neoplasia with an intrafollicular growth pattern. The neoplastic B cells are localized within the germinal center, without invasion of surrounding structures. In situ follicular neoplasia (Swerdlow et al., 2016), the newly adopted name for in situ follicular lymphoma, reflects low-risk of progression to overt lymphoma.
Alias: Follicular lymphoma-like B cells of undetermined significance (Fend et al., 2012). The term "Follicular lymphoma-like B cells of undetermined significance" has been proposed to indicate the unknown clinical outcome; Follicular lymphoma in situ (FLIS) (Jegalian et al., 2011); intrafollicular neoplasia /in situ follicular lymphoma (Harris et al., 2008); In situ localization of follicular lymphoma (Cong et al., 2002); Incipient follicular lymphoma (Pruneri et al., 2001); Follicular lymphoma of compartmentalized follicular center cells (Carbone et al., 1992).

An updated report of the case has recently been published under the title of "Coexisting follicular and mantle cell lymphoma with each having an in situ component" (Carbone and Gloghini, 2011).

Clinics and pathology

Disease

The 2008 "WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues" has addressed the problem of early lesions in lymphoid neoplasia (Harris et al., 2008; Swerdlow et al., 2008). In situ neoplasia has been recognized for both follicular lymphoma (FL) and mantle cell lymphoma (Richard et al., 2006; Aqel et al., 2008; Harris et al., 2008; Jares and Campo, 2008; Swerdlow et al., 2008; Pileri and Falini, 2009).
In the case of in situ follicular neoplasia the accumulation of neoplastic cells is detectable within the lymphoid follicles.
The follicular dendritic cells represent the barrier beyond which in situ follicular neoplasia does not extend (Carbone and Gloghini, 2014). In fact, the lesion follows the existing architecture of the involved lymphoid follicles. For these reasons, in situ follicular neoplasia does not usually form a tumor; it is not surprising, therefore, that these in situ lesions are often incidental findings in an otherwise reactive-appearing lymph node (Carbone and Santoro, 2011).

Epidemiology

Presently unknown

Without overt lymphoma	
Associated with overt lymphoma	
With overt follicular lymphoma (FL)	Early infiltration by synchronous FL
	or preceding FL by years
With lymphomas other than FL	splenic marginal zone lymphoma
	Classic Hodgkin Lymphoma
	Diffuse Large B-Cell Lymphoma
	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
	Lymphoplasmacytic lymphoma
	Peripheral T-cell lymphoma, unspecified
Associated with non lymphoid malignancies	
	Colorectal carcinoma
	Breast carcinoma
	Melanoma
	Lung carcinoma
	Other (sporadic reports)

Table 1. *In situ* follicular neoplasia: Clinical variants. Modified and adapted from Carbone et al., 2012.

Clinics

From a clinical point of view, in situ follicular neoplasia has an uncertain clinical behaviour and unknown risk to progression to overt lymphoma.
In terms of prognosis and treatment is important to rule out the presence of lymphoma in other locations and/or previously unknown non lymphoid malignancies (Carbone et al., 2012) (Table 1). To this end, a careful staging is advisable; this should include biopsy of additional lymph nodes or other suspicious tissue involvement, blood flow cytometry, and CT or PET scans

Pathology

The lymph node involved with in situ follicular neoplasia usually shows preservation of the nodal architecture, whereas a few follicles contain a monotonous population of small lymphoid cells and may lack tingible body macrophages. Affected follicles are usually scattered, and contain germinal center B cells that show strongly positive staining for BCL2 and CD10 (Cong et al., 2002; Harris et al., 2008; Carbone and Santoro, 2011) (Table 2). Pathological diagnosis of in situ follicular neoplasia requires recognizing strong immunostaining of BCL2 and CD10 by neoplastic B cells inside the affected follicles. In situ follicular neoplasia should be distinguished from overt follicular lymphoma with partial lymph node involvement. In this case partial effacement of the architecture could be observed (Campo et al., 2011; Jegalian et al., 2011; Fend et al., 2012).

Architecture	Intact
Follicle size	Normal
Distribution of involved follicles	Widely scattered
Follicular cuff	Intact
Follicular edge	Sharp
Expression of BCL2	Positive, very B
Expression of CD10	Positive, very B
Expression of CD20	Positive
Expression of BCL6	Positive
Expression of CD3	Negative
Follicular involvement	Usually limited to germinal center
Stromal microenvironment of the mantle	Intact

Table 2. *In situ* follicular neoplasia: Diagnosis s.Modified and adapted from Carbone and Gloghini, 2014.

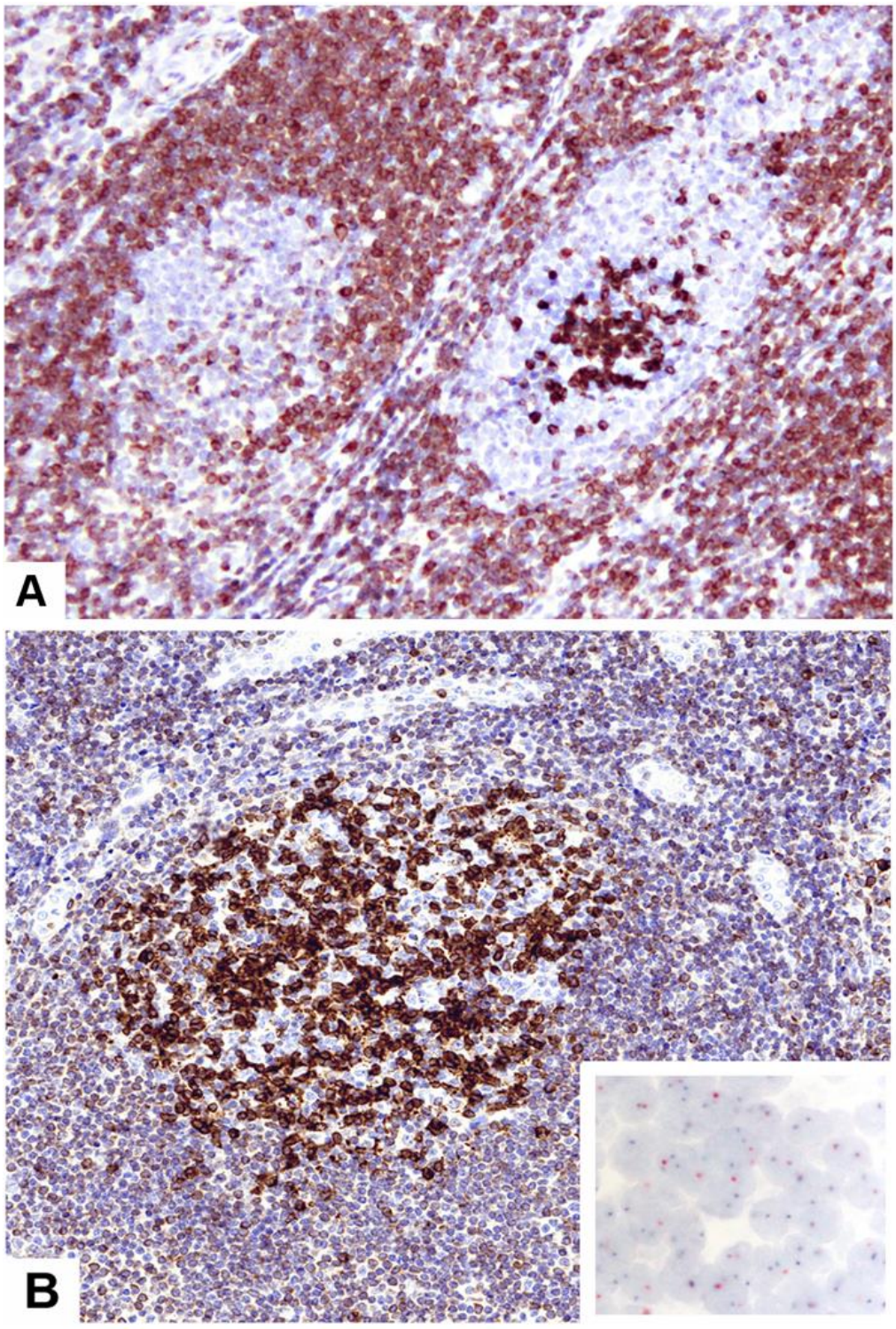

Figure 1. Various levels of germinal center involvement in in situ follicular neoplasia. The germinal center involvement ranges from few scattered BCL2+ B cells (A) to many BCL2+ B cells that occupy the germinal center (B). In all follicles, however, the BCL2+ B cells display a uniform and strong intensity of staining and are consistently restricted to germinal center, without invasion of the surrounding structures. (B Inset) Double-staining chromogenic in situ hybridization assay shows that cells in the affected follicle contain BCL2 split signals (i.e. clearly separate red and blue signals).(A, B) Immunohistochemistry, haematoxylin counterstain. (Inset) in situ hybridization, haematoxylin counterstain.

The proportion and distribution of the BCL2+ germinal center B cells within the affected follicles may be variable (Fig. 1), but the staining is consistently of strong intensity. BCL2 staining is stronger than in mantle cells or reactive T cells (Fig. 1). In all cases the neoplastic cells are localized and restricted to germinal centers without invasion of surrounding structures. Since follicular T cells are also BCL2+, an important step in evaluating BCL2 expression is to compare CD3 staining with BCL2 expression to control how many T cells are in the follicles (Carbone and Gloghini, 2014).

Treatment

The treatment depends on the coexistence or not of an overt lymphoma or other malignancies (Carbone et al., 2012) (Table 1): 1) in the case of localized in situ follicular neoplasia without evidence of overt disease a watchful waiting policy is recommended; 2) in the case of in situ follicular neoplasia with overt disease the treatment should be planned according to the site, stage and clinical characteristics of the patient (Cheson, 2008). For patients with concomitant overt malignancy, therapy must be applied according to the concomitant overt malignancy.

Genetics

Neoplastic cells of in situ follicular neoplasia are derived from germinal center B cells and display the genetic hallmark t(14;18) (q32;q21) (Sotomayor et al., 2007; Cheung et al., 2009).

In situ hybridisation analysis for t(14;18) (Fig. 1) is mandatory in doubtful cases in which immunohistochemistry data are ambiguous. Furthermore, a precise pathologic diagnosis of in situ follicular neoplasia may be corroborated by the demonstration of B-cell clonality, by microdissecting the BCL2+ follicles and analyzing them in parallel by PCR (Cong et al., 2002).

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