Ectopic extra-nodal in situ follicular neoplasia (ISFN)

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Dear Editor,

In situ follicular neoplasia (ISFN) is a rare WHO-recognized entity, which manifests in architecturally normal lymph nodes or other lymphoid tissues with one or more *bcl2*-positive follicular germinal centers suggestive of mature B cell follicular lymphoma (FL) [1]. We would like to bring attention to the first documented case in the literature of ectopic tonsil tissue partially involved by ISFN. One year ago, a 36-year-old woman underwent treatment for a pre-invasive endometrial endometrioid carcinoma, a well-known non-lymphoid malignancy. In order not to jeopardize the patient's fertility, hormonal treatment was adopted based on medroxyprogesterone acetate. The ectopic tonsil was extracted from the left Eustachian tube, since the patient complained of persistent auditory disturbance. Blood tests showed no significant abnormalities. Subsequent investigations revealed no occult FL (the patient is currently in follow-up). Given the uniqueness of this case, during the diagnostic phase, we performed the entire immunohistochemical panel for FL, including immunoglobulins of lymphocyte surface (IgG, IgM). In addition to germinal center immunopositivity for *bcl2*, *bcl6*, CD10, CD20, and CD23, a monotypic expression for IgM was detected

(Fig. 1), exactly as would be observable in the course of overt FL [2, 3]. The fluorescence in situ hybridization revealed the *IgH/BCL2-t(14;18)(q32;q21)* translocation, while the search for EBV antigens (EBER probe) resulted negative [4]. In challenging cases such as these, diagnosis should be performed by an expert hemolymphopathologist with immunohistochemical support. This is because ISFN entails four possible scenarios. (I) The patient may be affected by an underlying FL (near the site or elsewhere), the observed phenomenon being the colonization of pre-existing follicles by neoplastic germinal center cells [5]. (II) The patient may, in time, develop an overt FL, the observed changes being the expression of a pre-malignant condition [6]. (III) For the rest of the patient's life, no sign of progress towards FL may be apparent, and no sure explanation for the condition can be advanced [7]. (IV) The patient is affected by non-lymphoid malignancies [8]. For all the above reasons, ISFN diagnosis requires detailed analysis in the histopathological report, which should include precise indications for the patient's clinical management. It should also include an in-depth immunohistochemical description which assesses the presence of immunoglobulins of lymphocyte surface. In previous series, identified clonality was not univocally correlated with increased risk of overt FL [9]. The detection of concurrent alterations in germinal centers (*bcl2* immunopositivity and restricted Ig expression) and *bcl2* positivity alone should likewise not lead physicians to premature FL diagnosis, but a careful examination of the patient is mandatory. The above data could be of particular relevance to patients previously affected by malignancies and who underwent radio-/chemotherapy or hormone therapy.

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Fig. 1 Ectopic tonsil (a, H&E, 4×) partially involved by ISFN (b, CD20 clone L26, Ventana Roche, 4×): the immunoreaction for CD3 discharges the possibility of enrichment of T cells in the germinal center (c, Ventana Roche, 4×), while CD10 (d, Ventana Roche, 10×) and bcl6 (e, Ventana Roche, 4×) rule out colonization by marginal cells. The neoplastic follicles immunohistochemically show a strong bcl-2 positivity (f, black

arrows), which is contrariwise absent inside the reactive germinal centers (f, yellow arrows, Ventana Roche, 4×). MIB1 labeling discloses a diffuse pattern in the neoplastic follicles and a polarized pattern in the reactive ones (g, Dako, 4×). A monotypic expression for IgM has been detected only in the neoplastic germinal centers (h, black arrows), being absent in the non-neoplastic follicles (h, yellow arrows, Ventana Roche, 4×)

Compliance with ethical standards

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Conflict of interest The authors declare that they have no competing interests.

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