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Commentary

New Insight in a New Entity: NIFTPS and Valuable Role of Ancillary Techniques. The Role of PD-L1

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Since the time when, the endocrine pathology society meeting, held at the 2015 USCAP in Boston, suggested the change in the terminology for encapsulated/non-invasive (NI-FVPCs) and renamed them as "non-invasive follicular thyroid neoplasm" with papillary like nuclear features (NIFTP), several papers have been debating the controversial nature of them (Chen et al., 2012; Ganly et al., 2015; Liu et al., 2006; Lloyd et al., 2004; Nikiforov et al., 2016). This is also supported by the fact that NI-FVPCs, recently termed as NIFTPs, and invasive FVPT (I-FVPC), also known as encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), are not prognostically and molecularly alike (Bizzarro et al., 2016; Chen et al., 2012; Ganly et al., 2015; Liu et al., 2006; Lloyd et al., 2004; Maletta et al., 2016; Nikiforov et al., 2016; Ustun et al., 2014) as clearly assessed by several scientific reports demonstrating that I-FVPCs show more frequent lymph nodes metastases, recurrences and prevalence of *BRAF* mutations whilst NI-FVPCs (accounting for 50%–70% of the entire subset of FVPCs) show a more favorable outcome (Nikiforov et al., 2016). According to the paper by Nikiforov et al., this new entity was defined by an encapsulated nodule with a follicular architecture and a set of morphological features of PTC (including nuclear membrane irregularities, ground glass appearance of the nuclei, larger nuclear size) (Nikiforov et al., 2016). Given that, in these last months, several authors aim at the evaluation of additional histopathological features which may lead to a diagnosis of NIFTPs. Thus, ancillary techniques, including immunohistochemistry (IHC) and molecular markers are likely to assess the aggressive behavior and drive to the most appropriate clinical and/or surgical management. The recent prognostic role of programmed cell death ligand (PD-L1) expression on tumor cells was also correlated with a poor prognosis in thyroid cancers (Chowdhury et al., 2016). Specifically it has been highlighted that a high expression of PD-L1 in tumors is associated with tumor growth and metastatic behavior (Chowdhury et al., 2016).

In this issue of the *EBioMedicine*, Fu et al. evaluate their institutional experience with the expression of PD-L1 in EFVPTC and NIFTPs (Fu et al., 2017). They provided a classification of a retrospective cohort of 174 surgically resected thyroid nodules, from 2010 to 2015, including 40 benign lesions, 52 NIFTPs, 45 EFVPTCs and 37 LT cases of FVPTC with coexisting lymphocytic thyroiditis. According to other recent papers, these authors found that cytoplasmic PD-L1 levels were significantly lower in NIFTPs as compared to EFVPTCs ($p < 0.001$). Additionally cytoplasmic PD-L1 expression in NIFTPs was similar to the benign subgroup ($p = 0.554$). The increasing levels of PD-L1 in EFVPTC can play a significant role especially in the definition of the capsular invasion ($p < 0.001$). Not only the authors find higher levels in stage II or III EFVPTC but also a significant increase in patients with stage IV in correlation with high risk of aggressive disease, distant metastases or death. Another valuable data was offered by the evidence of as high expression of PD-L1 in cases with coexisting lymphocytic infiltration as it was found in the LT subgroup of FVPTC. Nonetheless, this yield emphasizes that a higher expression of PD-L1 should be interpreted with caution as long as it can be also associated with benign entities including chronic lymphocytic thyroiditis or Hashimoto's thyroiditis.

Importantly, Fu et al. did not find significant differences in cytoplasm PD-L1 expression between benign and NIFTPs supporting the suggestions that NIFTPs have been correctly defined as non-malignant neoplasms (Nikiforov et al., 2016). This data could also have a significant impact on the cytological evaluation of thyroid nodules in the differential diagnosis of NIFTPs versus EFVPTCs. In fact this is in agreement with the data from Maletta et al. and Bizzarro et al., who concluded that the majority of these NIFTPs are diagnosed as indeterminate lesions (Bizzarro et al., 2016; Maletta et al., 2016) on cytological samples. In this way, the data provided by Fu et al. on PD-L1 as useful marker in the discrimination between EFVPTC and NIFTP on histology could be also helpful on cytology, with important implications in clinical and surgical assessment and in lowering of the possible overtreatment.

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In conclusion, the morphological interpretation of the new terminology of NIFTP may be combined with ancillary techniques, i.e., PD-L1 analysis, in order to improve the accuracy of the histopathological diagnosis of NIFTPs, the clinical management and the long term follow-up.

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