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LETTER TO THE EDITOR
Synchronous and Metachronous Thyroid Cancer in Relation to Langerhans Cell Histiocytosis; Involvement of *V600E BRAF*-Mutation?

Langerhans cell histiocytosis (LCH) (cells identified in 1868, disease named in 1985), has a wide range of clinical presentations, including the rare event of infiltration of the thyroid gland. However, an association seems to exist between LCH and papillary thyroid carcinoma (PTC), as eight cases of LCH co-existing with PTC have been described in the english literature [1]. We extend this association with a metachronous case of PTC, occurring 4 years from the diagnosis of LCH, while the LCH was in remission (Table I).

In our case PTC was metachronous and not therapy related. This is verified by the fact that the patient did not receive etoposide or high doses of methotrexate, or local radiotherapy [2,3]. The radiation exposure was minimal; only two X-rays were performed at diagnosis, while imaging of the head was performed with MRI and no CT-scans. Therefore, a causative relationship is highly unlikely. More specifically, a 9-year-old boy, with low risk [RO-] LCH, *V600E BRAF* mutation positive, received vinblastine/prednisolone according to the LCH III protocol, and achieved remission. Four years following diagnosis of LCH, in the routine follow-up, an 8 mm lesion was revealed in the thyroid gland by ultrasound. Total resection of the thyroid gland revealed a *V600E BRAF* mutation-negative papillary carcinoma, while it was negative for LCH [SD100−, CD1a−, Langerin−].

No information exists on the *V600E BRAF* mutation status from the LCH cases co-existing with PTC [1]. In our case, the LCH sample was positive for the *V600EBRAF* mutation, while the PTC was negative for the mutation. It is possible that LCH and PTC share a common determinant, despite the different *BRAF* mutation status, as approximately half of the reported cases of LCH are negative for the mutation and only around half of the reported PTCs are positive for the mutation [4]. The role of the *V600E BRAF* mutation is currently unknown. One could speculate that, since the LCH has been shown to increase the expression of T-helper type 2 cytokines [5], the presence of the *V600E BRAF* mutation could exacerbate this defect in LCH cytokine regulation. Thus, the particular oncogene might be eliciting an inflammatory pro-tumorigenic microenvironment, possibly linking the LCH-induced deregulated immunologic cascade to neoplastic transformation. It would be of great interest to have more information on the *BRAF* mutation status from cases of LCH co-existing with PTC, as it would help to elucidate the role of *V600E BRAF* mutation in PTC development.

In summary, the thyroid gland is a potential target organ for LCH, both through direct involvement of the disease and through its association with the development of thyroid carcinoma. Thus, routine evaluation of the thyroid gland at diagnosis and during follow-up should be considered. Further research is needed to understand the association of LCH with PTC, as well as the molecular and immunological basis for this tropism to the thyroid gland.

TABLE I. Time of Presentation of Papillary Thyroid Carcinoma (PTC) in Relation to the Diagnosis of LCH

	Case reference	Age/sex	Case description
Synchronous	Vergez *et al* (2010) [1]	37yr/F	Simultaneous presentation of PTC and LCH
		31yr/F	Thyromegaly secondary to simultaneous PTC and LCH
		38yr/F	Simultaneous presentation ofPTC and LCH
		43yr/M	LCH in association with a small focus of papillary carcinoma
		42yr/F	LCH confined to the thyroid and associated with lymphocytic thyroiditis and a papillary microcarcinoma
		3yr/M	Case presented with goiter; simultaneous presentation of LCH with PTC
		24yr/M	Invasive papillary cancer of the thyroid simultaneously with LCH
		29yr/M	Bone, lung, skin, thyroid, and hypothalamo-pituitary LCH lesions with concomitant presentation of PTC
Metachronous	Moschovi *et al* (present letter)	9yr/M	Thyroid cancer appearing 4 years following diagnosis of LCH, while the patient was in complete remission

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