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 V600E BRAF 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 of PTC 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           |
|                         | 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            | 9yr/M   | Thyroid cancer appearing 4 years following diagnosis of LCH, while the patient was in complete remission |

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided that the article is properly cited.

© 2014 The Authors. Pediatric Blood & Cancer, published by Wiley Periodicals, Inc.
DOI 10.1002/pbc.25173
Published online 22 August 2014 in Wiley Online Library (wileyonlinelibrary.com).
REFERENCES

1. Vergez S, Rouquette I, Ancey M, et al. Langerhans cell histiocytosis of the thyroid is a rare entity, but an association with a papillary thyroid carcinoma is often described. Endocr Pathol 2010;21:274–276.

2. Haupt R, Fears TR, Heise A, et al. Risk of secondary leukemia after treatment with etoposide (VP-16) for Langerhans’ cell histiocytosis in Italian and Austrian-German populations. Int J Cancer 1997; 71:9–13.

3. Haupt R, Nanduri V, Calero MG, et al. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society-Late Effects Study Group. Pediatr Blood Cancer 2004;42:438–444.

4. De Biase D, Cisari V, Visani M, et al. High sensitivity BRAF mutation analysis. BRAF v600E is acquired early during tumor development but is heterogeneously distributed in a subset of papillary thyroid carcinomas. J Clin Endocrinol Metab 2014; jct20134389.

5. Tsuji Y, Kogawa K, Imai K, et al. Evans syndrome in a patient with Langerhans cell histiocytosis: possible pathogenesis of autoimmunity in LCH. Int J Hematol 2008;87:75–77.