Langerhans Cell Histiocytosis, Non-Langerhans histiocytosis and concurrent Papillary Thyroid Carcinoma with BRAF V600E mutations: A case report and literature review

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1. Introduction

Langerhans Cell Histiocytosis (LCH) and the non-LCH, Erdheim Chester Disease, are rare histiocytic neoplasms with distinctive clinical and immunophenotypic features, but with several overlapping molecular features. LCH is a neoplasm of Langerin-positive, CD1a-positive, S100-positive dendritic cells (DCs), once thought to arise from the epidermal or mucosal-derived Langerhans Cell (LC) due to the morphologic, immunophenotypic, and ultrastructural similarities between neoplastic LCH cell and the physiologic LC \cite{5,6}. However, gene expression profiling studies of LCH cells have shown that these cells are not derived from terminally differentiated LCs as originally thought, but rather share a closer kinship with dendritic cells of the bone marrow than with LCs of the skin \cite{5-7}. LCH presents most often as a solitary lesion involving the bone, lymph node, skin or lung, but may also present with multifocal lesions or multisystemic disease, additionally involving the liver, spleen and bone marrow. Although LCH displays a broad spectrum of clinical presentations, histologically, all lesions include prototypic LCH cells in an inflammatory background, often with admixed eosinophils and T-cells, leading those who originally studied the disease to question the neoplastic versus the reactive or inflammatory nature of the lesion \cite{8}.

One of the most common non-LCH histiocytoses, Erdheim Chester Disease (ECD), is a rare multisystem neoplasm of adults diagnosed via a combination of clinical, radiological and pathological findings, with consensus diagnostic criteria requiring detection of the typical neoplastic cells and nearly constant skeletal involvement \cite{9-11}. The neoplastic cells are foamy histiocytes that express CD14, CD68 and CD163, rarely S100, and are negative for
CD1a and Langerin and are often admixed with Touton giant cells and other reactive cells [12]. ECD may also involve multiple sites, similar to LCH. ECD patients commonly present with retroperitoneal, renal and/or cardiac involvement, and have a historically poor overall survival (median 3 years), often with progressive neurodegenerative disorders [10].

Molecular studies have detected recurrent BRAF and MAPK pathway-activating mutations in both of these neoplasms, with BRAF mutations present in up to 69% of LCH and in 82% of ECD [4]. These findings have led researchers to believe that LCH and ECD may be clonally related disorders, and may theoretically arise from a primitive common progenitor, supported by the fact that these neoplasms occasionally co-occur. Approximately 20% of patients with LCH also present with non-LCH either subsequently or simultaneously, even within the same biopsy site, a phenomenon known as “mixed histiocytosis” (MH) [2-4]. LCH and non-LCH may also co-occur with non-hematopoietic neoplasms, including Papillary Thyroid Carcinoma (PTC), approximately half of which have activating BRAF mutations [13-32]. Although rare cases of concurrent histiocytosis and PTC exist, most reports have not documented the BRAF status of the lesions.

Herein we present a case of a 39-year-old female with LCH and non-LCH involving a left neck soft tissue mass, as detected in two biopsy specimens, along with a separate, but concurrent, Papillary Thyroid Carcinoma, all harboring the canonical BRAF V600E mutation. We discuss this unique case to illustrate the relationship between LCH and non-LCH lesions and explore their connections with tumors of different cellular origins. We also review the literature to document the prevalence of these lesions and their mutations, and to gain insight into the role that molecular drivers like BRAF play in histologically diverse tumors.

2. Case report

The patient is a 39-year-old female in previously good health who presented to her physician with a three-week history of a palpable anterior left neck mass. A PET scan revealed a 2 cm FDG-avid left cervical neck soft tissue mass and two non-avid left thyroid nodules. The patient underwent a fine needle aspirate (FNA) of the thyroid nodules, which showed atypia of undetermined significance (AUS). A needle core biopsy of the left neck soft tissue mass revealed LCH. The patient subsequently underwent a total thyroidectomy and excisional biopsy of the left neck mass. Normal thymic tissue was biopsied as part of this procedure. The thyroidectomy specimen was significant for two small foci of PTC in the left-lobe, positive for the BRAF V600E gene mutation. Interestingly, the left neck excisional biopsy revealed a non-LCH histiocytic/dendritic cell neoplasm, and molecular studies were positive for the BRAF V600E gene mutation. Mutational analysis of thymic tissue resected at the time of surgery was negative for the BRAF mutation, confirming the somatic nature of the BRAF mutations in the thyroid and histiocytic lesions.

Clinically, the patient has been doing well since surgery with no other treatment. A recent PET scan showed no abnormalities or masses except slight uptake in the bilateral tonsils, thought to be reactive in nature.
3. Methods

3.1. Histology and immunohistochemistry

Routine sections of formalin-fixed paraffin-embedded (FFPE) tissue from the first left neck needle-core biopsy, the subsequent left neck excisional biopsy, the thyroidectomy and the thymus biopsy were stained with Hematoxylin and Eosin (H&E) and microscopically examined. Immunohistochemical (IHC) stains were performed and included CD79a (Roche), CD3 (Ventana), CD68 (Roche), CD1a (Roche), Langerin/CD207 (Leica), CD163 (Roche), BRAF VE1 (Ventana), Cyclin D1 (Roche) and Ki67 (Dako). The BRAF VE1 antibody clone is specific for the BRAF V600E mutant protein [33].

3.2. Molecular analysis

DNA was extracted from microdissected FFPE tissue sections of both the initial left neck excisional biopsy and the papillary lesion of the thyroid using the Qiagen QIAamp DNA FFPE Tissue Kit. The DNA was diluted to an appropriate concentration and subjected to droplet digital PCR for the detection of BRAF V600E (C.1799C > A) using a Bio-Rad QX200 Droplet Digital PCR System. Following droplet generation in the QX200 droplet generator, PCR was performed in a 96 well microtiter plate with a single primer set encompassing position c.1799 of the BRAF gene. Amplification products were detected with two allele specific competitive probes, one to wild type sequence c.1799 T (labeled with HEX), and a second to the mutant sequence of C.1799A (labeled with FAM). Individual droplets were analyzed in the QX200 droplet reader using a two-color fluorescent detection system and quantitation of the mutant allele fraction was performed with QuantaSoft software.

4. Results

4.1. Histology and immunohistochemistry

Microscopic examination of H&E sections of the initial left neck needle-core biopsy revealed an infiltrate of diffuse, non-cohesive monomorphic cells with folded nuclei and abundant eosinophilic-to-finely-vacuolated cytoplasm (Fig. 1A). A polymorphous population of small mature lymphocytes, a few plasma cells and eosinophils were also present. The cells were positive for Langerin (Fig. 1B), CD1a and BRAF VE1, and were negative for CD163 and the other stains. The findings were diagnostic of LCH.

H&E sections from the subsequent left neck excisional biopsy showed medium-to-large monomorphic cells with ovoid nuclei, vesicular chromatin, inconspicuous nucleoli and abundant finely vacuolated eosinophilic cytoplasm (Fig. 2A). The cytological features differed from the prior biopsy in that the atypical cells had mostly round-to-oval nuclei, lacking the lobulated and indented nuclei of the LCH lesion. In addition, cytoplasmic vacuolation was more conspicuous. By IHC, the cells were positive for S100, Cyclin D1, CD163, CD68 and BRAF VE1, but only rare cells were positive for CD1a, and Langerin was negative (Fig. 2B-D). A diagnosis of non-LCH histiocytic/dendritic cell neoplasm was rendered.
Most H&E sections of the thyroid biopsy showed unremarkable thyroid follicles with no significant inflammatory component. However, two separate foci (0.5 cm and 0.1 cm) of papillary proliferations composed of atypical cells with clear cytoplasm were present within the left lobe, consistent with PTC (Fig. 3A). The BRAF VE1 IHC stain was positive in these cells (Fig. 3B). The thymic biopsies revealed hyperplastic thymic tissue, without evidence of histiocytosis or PTC.

4.2. Molecular analysis

Adequate DNA was obtained from the left neck mass, the thyroid and the thymus biopsies for BRAF mutation analyses. The percentage of tumor cells in the left neck biopsy sample was estimated between 25 and 30% and the c.1799 T > A (BRAF V600E) mutation was detected at an allele fraction of 3.38%. The percentage of tumor cells from the lesional thyroid tissue sections was estimated between 15 and 20%. The c.1799 T > A (BRAF V600E) mutation was detected at an allele fraction of 6.8%. Mutational analysis of the thymus did not detect the c.1799 T > A (BRAF V600E) mutation.

5. Discussion

We present a case of a young woman with concurrent LCH, non-LCH and PTC. The lesions were diagnosed concordantly but were physically separate lesions. The histiocytosis did not involve the thyroid and the PTC showed no evidence of lymph node involvement. The histiocytic lesions, sampled weeks apart from the same site, were phenotypically dissimilar in their expression of histiocytic IHC markers, although both lesions expressed the BRAF VE1 mutant protein, which is specific for the BRAF V600E gene mutation. The PTC was also positive by BRAF VE1 IHC, and molecular studies revealed that both the non-LCH histiocytic lesion and the PTC had identical BRAF mutations, while the uninvolved thymic tissue did not, confirming the somatic nature of the mutations.

This case reinforces the association between LCH and non-LCH lesions and highlights the unique association between BRAF-positive histiocytic lesions and BRAF-positive carcinomas, an occurrence that has not been well described in the literature, and which deserves a closer look.

Although LCH and non-LCH lesions originally comprised separate histologic categories attributed to differences in their clinical presentation, immunophenotype and presumptive cellular origin (Langerhans dendritic cell vs. non-LC histiocyte), we now understand that these disorders overlap, which refutes the historically strict LCH/non-LCH dichotomy. Approximately 20% of patients with these disorders present with mixed histiocytosis (MH) [2-4], similar to the findings in our patient's biopsy. The Revised Classification of Histiocytoses by Emile et al proposes to reclassify histiocytic lesions into categories based on clinical presentation, radiographic findings, pathological phenotype, and genetic and molecular alterations. In their schema, LCH, along with ECD, are included within the same group (Group L) due to their overlapping genetic, molecular and clinical features [3].

These clonal disorders are both driven by activation and over-activation of normal cellular signaling due to mutations of MAPK pathway proteins [2-6,8,10,34-37]. This signaling
cascade, which consists of RAS-RAF-MEK (MAPK)-ERK, contributes to cellular survival, proliferation and differentiation [1]. Mutations in the critical pathway regulator, BRAF, comprise the largest percentage of MAPK pathway abnormalities, present in up to 69% of LCH and in 82% of ECD [4]. The activating BRAF point-mutation c. 1799 T > A leads to a V600E amino acid change, which allows the mutant BRAF protein to function independently from RAS, and results in constitutive pathway activation through downstream MEK and ERK activation [35]. In addition, recent studies have shown that nearly all of LCH and ECD patients lacking the BRAF mutation have abnormalities in other MAPK pathway regulators, including MAP2K1, ARAF, N/KRAS or one of the other pathway regulators [2,36-38].

LCH and non-LCH may also co-occur with non-hematopoietic neoplasms, including non-small cell lung carcinoma, colonic adenocarcinoma and PTC [13-32], as we have described here. Twenty-one previously reported cases of concurrent LCH and PTC exist in the English literature, including the current case, although most did not report the BRAF mutational status of the PTC (Table 1). One case reported the BRAF mutation status of both the LCH and PTC, but found discordant mutation results (BRAF-positive LCH and BRAF-negative PTC) [13]. To date, there is only one other documented case of coexisting LCH, non-LCH and PTC with concurrent positive BRAF mutations [39]; that patient had more extensive disease, with both bone and soft tissue involvement by the non-LCH (ECD), as well as cutaneous involvement by LCH.

While the exact effects of the BRAF mutation are still unknown, its disturbance of normal cell signaling may exacerbate the defect in cytokine regulation within LCH cells. Normal activated LCs increase the expression of T-cell pro-inflammatory cytokines, a characteristic also observed in neoplastic LCH cells operating outside normal homeostatic control [5,40]. Through unchecked activation, the oncogene may be generating an inflammatory protumor microenvironment, thereby promoting its own existence as well as providing an ideal milieu for the neoplastic transformation of neighboring cells [13]. Conversely, an initiating inflammatory event may produce reactive oxygen species, acting as a mutagenesis in bystander LCs and nearby epithelial cells. It is also possible that these mechanisms feed off each other, leading to an unstable cycle, or contribute via more complex, and as of yet, unknown interactions.

Supporting the theory of interdependent microenvironmental factors is the recognition that patients with inflammatory conditions are at a higher risk of developing certain neoplasms. For example, patients with inflammatory bowel disease have an increased incidence of colonic adenocarcinoma compared with the general population, and patients with cutaneous inflammatory disease have an increased incidence of melanoma, both of which show activation of MAPK pathways [6]. Although there was no evidence of thyroiditis in our case nor in that reported by Johnson et al [39], it is reported that patients with lymphocytic thyroiditis have a higher risk of PTC, and this association has been described in case reports of patients with coexisting LCH and PTC [14]. Additional studies will be useful to help further define the role the microenvironment may play in the development of these disorders.
In summary, LCH and ECD are rare histiocytic neoplasms with distinctive clinical and immunophenotypic features, and with overlapping molecular features involving activating mutations of *BRAF* and *MAPK*. We have reported a novel case with phenotypically diverse lesions, but sharing a common mutational profile, indicative of a clonal relationship. These observations provide further evidence that LCH and ECD are derived from a common myeloid progenitor. In rare instances, LCH and ECD may occur with another neoplasm such as PTC, also manifesting a *BRAF* mutation. The root cause for this association is still unknown, but the number of similar reports in the literature suggests that the association is not random. Recent research is focusing on the association between inflammation, the microenvironment and neoplasia within the context of MAPK pathway mutations, as well as on emerging theories of progenitor cell mutagenesis and lineage plasticity. All of these theories are intriguing and deserve further exploration and study.

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Fig. 1. Left neck mass, Needle-core biopsy.
Sections show sheets of large cells with folded nuclei and abundant eosinophilic cytoplasm, positive for Langerin (CD207) immunohistochemistry, consistent with a diagnosis of Langerhans Cell Histiocytosis. A. H&E (20 ×); Inset H&E (60 ×); B. Langerin (40 ×).
Fig. 2. Left neck mass, Excisional biopsy.
The biopsy shows cells with ovoid nuclei and abundant finely vacuolated
eosinophilic cytoplasm, negative for Langerin and positive for CD68 and BRAF VE1
immunohistochemical stains. A. H&E (40×); B. Langerin (40×); C. CD68 (40×); D. BRAF
VE1 (40×).
Fig. 3. Thyroidectomy.
A small focus of Papillary Thyroid Carcinoma is present in the left lobe, positive for BRAF VE1 immunohistochemical stain. A. H&E (40×); B. BRAF VE1 (40×).
# Table 1

Case reports in the English literature of co-existing LCH and/or non-LCH and PTC.

| Author (Reference) | Year | Patient | Disease | Synchronous/ metachronous | BRAF status |
|--------------------|------|---------|---------|---------------------------|-------------|
| Hershkovitch [18]  | 1989 | 37 yo F | LCH-Multisystem PTC | Synchronous | NA          |
| Goldstein [19]     | 1991 | 31 yo F | LCH-Multisystem PTC | Synchronous | NA          |
| Schofield [20]     | 1992 | 55 yo M | LCH-Thyroid PTC | Synchronous | NA          |
| Thompson [21]      | 1996 | 38 yo F | LCH-Thyroid PTC | Synchronous | NA          |
| Safali [22]        | 1997 | 51 yo M | LCH-Thyroid/LN PTC | PTC 1st, LCH 8 years later | NA          |
| Lindley [23]       | 1998 | 22 yo F | LCH-Thyroid/LN PTC | PTC 1st, LCH 2 months later | NA          |
| Saiz [24]          | 2000 | 43 yo M | LCH-Thyroid PTC | Synchronous | NA          |
| Foulet-Roge [25]   | 2002 | 42 yo F | LCH-Thyroid PTC | Synchronous | NA          |
| Burnett [26]       | 2006 | 3 yo M  | LCH-Multisystem PTC | LCH 1st, recurrent LCH and PTC 4 years later | NA          |
| Jamaati [15]       | 2009 | 24 yo M | LCH-Multisystem PTC | Synchronous | NA          |
| Vergez [14]        | 2010 | 29 yo M | LCH-Multisystem PTC | Synchronous | NA          |
| Guarino [16]       | 2013 | 22 yo F | LCH-Pituitary PTC | Synchronous | NA          |
| Ceyran [27]        | 2014 | 37 yo M | LCH-Thyroid PTC | Synchronous | NA          |
| Bucau [28]         | 2015 | 52 yo F | LCH-Multisystem PTC | Synchronous | NA          |
| Moschovi [13]      | 2015 | 9 yo M  | LCH-Thyroid PTC | LCH 1st, PTC 4 years later | LCH + PTC – |
| Gordon [29]        | 2016 | 22 yo F | LCH-Multisystem PTC | PTC 1st, LCH 3 years later | NA          |
| Kuhn [30]          | 2016 | 73 yo F | LCH-Thyroid | NA | NA          |
| AlZahrani [31]     | 2016 | 27 yo F | LCH-Thyroid PTC | Synchronous | NA          |
| Wu [32]            | 2017 | 40 yo M | LCH-Multisystem PTC | Synchronous | NA          |
| Johnson [39]       | 2016 | 38 yo F | LCH- Skin Non-LCH(ECD)-Multisystem PTC | Synchronous | LCH + Non-LCH + PTC + |
| Wake (current report) | 2018 | 39 yo F | LCH-soft tissue Non-LCH-soft tissue PTC | Synchronous | LCH + Non-LCH + PTC + |

NA = Data not available; LCH = Langerhans Cell Histiocytosis; ECD = Erdheim Chester Disease; PTC = Papillary Thyroid Carcinoma.