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Clinical Medicine Insights: Case Reports

Association between Pituitary Langerhans Cell Histiocytosis and Papillary Thyroid Carcinoma

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ABSTRACT: Here we report a case of panhypopituitarism caused by pituitary Langerhans cell hystocitosis (LCH) in a 22-year-old woman affected by papillary thyroid carcinoma (PTC). Although several cases of the coexistence of PTC and LCH within thyroid tissue have been described in relative literature, in this case, the patient presented a unique suprasellar retrochiasmatic histocytosis localization which, to the best of our knowledge, had never been described before in association with PTC. Even if this aspect is not addressed in the present case report, it is worth noting that about 50% of the patients affected either by LCH or PTC are characterized by activating mutations of the proto-oncogene *BRAF*. This, along with other clinical studies, may warrant further biomolecular large-scale case study investigations in order to evaluate a possible connection between the 2 conditions and shed light on the etiology of these diseases, which are still largely unknown.

KEYWORDS: papillary thyroid carcinoma, Langherans cell hystiocytosis, hypopituitarism

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Introduction

Papillary thyroid carcinoma (PTC) is a well-differentiated epithelial neoplasm originating from follicular thyroid cells.[1] It represents the most common malignant endocrine neoplasia accounting for about 1% of all human cancers, being the fifth most common cancer among women in the United States.[1,2] Besides radiation, no other etiologic factor for PTC is known. However, early genetic mutations involved in PTC, comprise, among others, gene rearrangements of tyrosine kinase receptors, such as the RET/PTC and NTRK1 (neurotrophic receptor-tyrosine kinase 1), or activating point mutations of the proteins mediating cellular responses to growth factors, including RAS and BRAF.[3] PTCs manifest themselves as nodules, and diagnosis relies on patients' clinical parameters, ultrasonography (US), and fine needle aspiration cytology.[4–7] Early lymphatic invasion represents a preferential route of metastases for this type of malignancy, explaining the high incidence of cervical locoregional lymph nodes spread.[1–5] The accurate diagnosis of locoregional lymph node metastasis is also of primary importance for the initial surgical approach as well as for patients' prognoses.[8–10] Although the latter is most favorable, with a 10-year survival rate of nearly 90%, roughly 20% of patients face disease recurrence and PTC-related deaths.[11,12] The recent identification of new molecular markers like uPA, uPAR, and $BRAF^{V600E}$ used on patients affected by PTC is thought to improve the actual staging system of PTC patients, permitting a better assessment of disease aggressiveness, risk stratification, and postoperative decision making tailored to single patient needs.[13–15]

Langerhans cell histocytosis (LCH) is a group of clinical conditions of unknown etiology characterized by clonal proliferation of bone marrow Langerhans-like cells either

in situ, leading to isolated bone lesions or, having spread in different remote tissues, potentially capable of inducing multisystem disease.[16,17] Whether LCH should be considered a reactive disorder or a real malignancy is, however, still a matter of debate.[18–21] LCH of the central nervous system is considered an important and permanent consequence in patients with LCH of the craniofacial bones as these are connected by circumventricular organs to the pituitary and hypothalamic regions.[22,23] We report here the case of a young woman affected by suprasellar hypothalamus LCH and PTC.

Methods

Ultrasonography (US) and US elastography of the thyroid nodule. Conventional ultrasonography (US) of the thyroid was performed using the Aplio XV (Toshiba, Japan) system equipped with a linear transducer (PLT-805AT). US elastography (USE), assessing the elasticity of thyroid tissue in vivo, was carried out using the Accuvix A30 (Samsung Medison Italia srl, Italy) calculating the elastography contrast index (ECI) as previously described.[24,25]

Fine-needle aspiration cytology (FNAC) and histopathology of the thyroid nodule. The FNAC and histopathology were performed, as previously described, with cytological and histopathological diagnoses defined according to widely recognized guidelines.[26,27]

Case Report

A 22-year-old Caucasian woman came to our surgery department with a suspected thyroid-mass malignancy. From the anamnesis, we learned that the patient had had a 2-year history of amenorrhoea, polyuria, polydipsia, and diplopia, suggesting a panhypopituitarism, which was confirmed by the analysis of hormone serum levels. The patient was on hormonal replacement therapy and on vasopressin analogue. No familiar diseases were reported, and the patient did not report any previous significant disease. About 6 months before admission to our unit, the patient underwent an enhanced magnetic resonance image (MRI) of the head that revealed an oval-shaped suprasellar lesion (diameters 17 mm × 8 mm) with involvement of the median and paramedian left hypothalamus (Fig. 1). The patient was then admitted to a neurosurgery unit where a positron emission tomography/computed tomography (PET-CT) confirmed the presence of a 2-cm suprasellar oval-shaped neoplasm right behind the optic chiasm suspected of being a papillary craniopharyngioma; no other lesions were documented. The patient then underwent a craniotomy with multiple biopsies taken from the lesion since it was found unresectable due to local invasion of the surrounding structures. The histopathology study revealed the presence of LCH within the biopsied tissues. During the same period, the patient also underwent an ultrasound examination for a suspicious thyroid mass that revealed the presence of a nodule (diameters 42 mm × 33 mm × 25 mm) within the right lobe that was isoechoic with some hypoechoic areas (Fig. 2, left side). When admitted to our department, a US-elastography (Fig. 2, right side) of the lesion was performed. It appeared stiff with a high ECI index suggesting its malignant nature.[24,25] An ultrasound-guided fine needle aspiration (FNA) of the nodule revealed the presence of suspicious malignant cells according to the Bethesda system for reporting thyroid cytopathology.[27] For this reason, the patient underwent a total thyroidectomy, which was complicated by right recurrent nerve palsy due to surgical trauma as a result of the dense adhesions in the right nodule despite an accurate surgical identification of the recurrent laryngeal nerve. This required admission to a postoperative high dependency unit and speech therapy. The histopathology report revealed the presence of a papillary carcinoma of the thyroid with local infiltration of the thyroid capsula staging pT3N0M0, with no sign of LCH infiltration (Fig. 3).[4,5]

To rule out any other localizations of LCH, the patient underwent a postoperative MRI of the abdomen, which was negative. The patient then underwent radioiodine treatment and appropriated hormonal replacement therapy. Five months

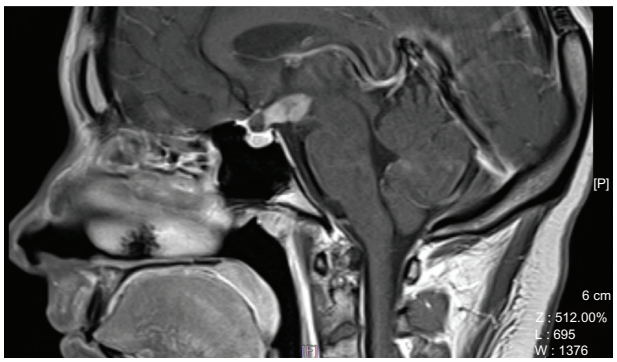

Figure 1. Magnetic resonance imaging of the suprasellar lesion. Sagittal plane showing the presence of oval-shaped lesion (diameters 17 mm × 8 mm) in the suprasellar region. The lesion presents intense enhancement with a central hypointense area.

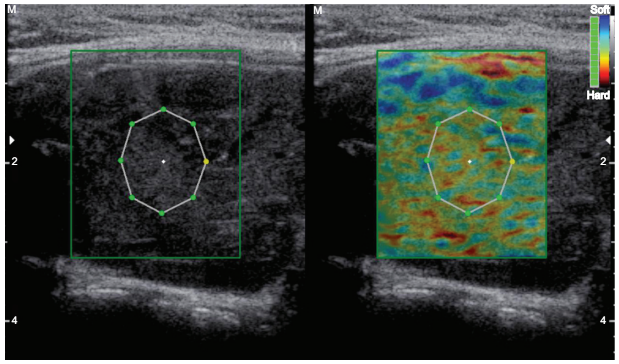

Figure 2. Ultrasonograpgy (US) and US-elastography of the thyroid nodule. Baseline US showed a large hypoechoic nodule (diameters 42 mm × 33 mm × 25 mm) with fairly marginated margins (left side); at US-elastography (right side) the lesion appeared stiff with a high ECI index suggesting its malignant nature.

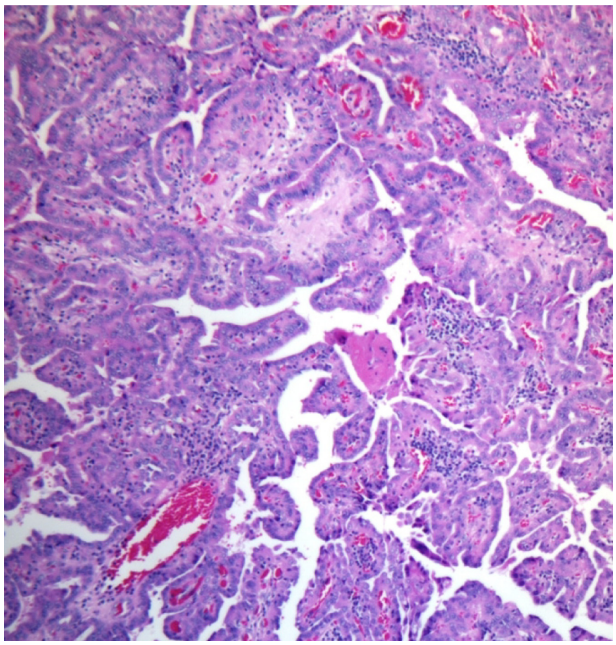

Figure 3. Histology of the thyroid nodule. Typical thyroid papillary carcinoma containing numerous branching and randomly oriented papillae, with a central fibrovascular core lined by a single epithelial cells showing ground glass nuclei and nuclear groove.

after the thyroidectomy, the patient presented a stable LCH mass, appropriate hormonal control, and a fully recovered voice.

Discussion

We have presented here the case of a young woman affected by PTC associated with isolated suprasellar LCH causing panhypopituitarism. In the literature, several cases of PTC and LCH coexistence have been described.[28–30] In the present case, however, the patient presented a unique localization of the histocytosis: suprasellar retrochiasmatic. To the best of our knowledge, no cases in the literature have reported to date of the coexistence of a cerebral LCH and PTC. Although the above clinical evidence may suggest an association between the 2 diseases, the existence of an etiopathogenetic link between the 2 pathologies remains to be established. As mentioned above, the etiology of LCH is still largely unknown. Interestingly, a previous epidemiological study aimed at investigating the potential risk factors associated with LCH found a significant association between LCH and thyroid disease of the proband with an odds ratio of 21.6.[31] It may also be worth noting that both LCH and PTC patients are characterized, in about 50% of cases, by somatic activating mutations of the proto-oncogene *BRAF*.[6,32] Thus, even if not addressed in the present study, the presence of an etiologic factor(s) capable of inducing *BRAF* mutation in different tissues may be conjectured. We believe that further biomolecular large-scale studies should be specifically addressed in order to evaluate the possible connections between these 2 conditions. Moreover, it has to be noted that the characterization of *BRAF* status may turn out useful in both LCH and more aggressive PTC treatments using specific *BRAF* inhibitors. In view of the increasing incidence of PTC, especially in women, one possible clinical implication of these findings is that patients with LCH characterized by activating *BRAF* mutations should be monitored for PTC.

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Author Contributions

AC conceived and designed the experiments. SG, DMG, AR, CF, VDA, FMDM, PF analysed the data. AC wrote the first draft of the manuscript. AC, VDA, FMDM, PF contributed to the writing of the manuscript. SG, DMG, AR, CF, VDA, FMDM, AC agree with manuscript results and conclusions. SG, DMG, AR, CF, VDA, FMDM, AC, EDA jointly developed the structure and arguments for the paper. SG, DMG, AR, CF, VDA, FMDM, AC, EDA made critical revisions and approved final version. All authors reviewed and approved the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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