Solitary Langerhans Histiocytosis of the Thyroid Gland: A Case Report and Literature Review

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Abstract Langerhans cell histiocytosis (LCH) is a rare disease of antigen presenting cells, with an incidence rate of 4.0–5.4 per 1 million individuals. The most common endocrinological manifestation of classical LCH is associated with the posterior pituitary, presenting as Diabetes Insipidus. However, LCH can affect multiple organs and classification is based on the body system involvement. The disease is confirmed by electron microscopy or immunohistochemical reactivity of histiocytes to CD1a and/or S100. LCH rarely involves the thyroid gland, and management of such disease is controversial. Current literature documents 65 English language reported cases of LCH involving the thyroid gland. We present an unusual case of LCH of the thyroid gland, with variable diagnoses on fine needle aspiration (FNA) cytology, and literature review of all English reported cases.

Keywords Thyromegaly · Thyroid gland tumour · Langerhans cell histiocytosis · Langerhans cell histiocytosis of the thyroid gland

Introduction

Langerhans cell histiocytosis (LCH) is a rare neoplastic disease of antigen presenting cells, with an incidence rate of 4.0–5.4 per 1 million individuals [1]. The most common endocrinological manifestation of classical LCH is associated with the posterior pituitary, presenting as Diabetes Insipidus (DI) [1]. However, LCH can affect multiple organs and classification is based on the body system involvement [2]. The disease is confirmed by electron microscopy (less commonly used today) or immunohistochemical reactivity of histiocytes to CD1a and/or S-100 protein [3]. LCH rarely involves the thyroid gland, and management of such disease is controversial. Current literature documents 65 English language reported cases of LCH involving the thyroid gland (Table 1). We present an unusual case of LCH of the thyroid gland, with variable diagnoses on fine needle aspiration (FNA) cytology, and literature review of all English reported cases.

Case

A 44-year-old lady, with globus symptoms and dysphonia, presented to clinic with a 3-month history of a left-sided anterior neck swelling. Clinical examination revealed a firm painless left thyroid lobe and laryngoscopy did not identify any structural or functional abnormality of the vocal folds. The patient had no known drug allergies and was receiving levothyroxine hormone replacement therapy for (antibody negative) hypothyroidism. There was no additional past medical or surgical history.

An ultrasound scan (USS) of the neck, conducted at the referring hospital, reported an enlarged (3 cm in diameter) left thyroid lobe. Subsequent FNA cytology results

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Table 1 Reported cases of langerhans cell histiocytosis involving the thyroid gland (in chronological order)

Patient age (years)/gender	Clinical features and biochemical status of the thyroid gland	Other organ involvement	Treatment	Survival	Author
<i>Article in French</i>					
11/M	Diffusely enlarged firm goitre	NR	NR	NR	Panayotopoulos et al. [4]
8.5/F	Firm goitre, dec T4, dec RAI uptake	OM, DI	Dessicated thyroid, pitressin	NR	Wilkins [5]
19/M	Goitre, (N) TSH, (N) T4, RAI uptake in right lobe only	DI, skin, exertional dyspnoea	ST	NR	Whitaker et al. [6] Rothman et al. [7]
20/M	Enlarged, smooth, diffuse goitre; (N) TSH, (N) T4	Interstitial lung disease, DI, hidradenitis suppurativa	ST, levothyroxine, lypressin, prednisolone	NR	Mahzoon et al. [8]
2.25/M	Irregular, firm goitre; inc TSH, dec T4	Seborrhea, migratory rash, DI, OM	DDAVP, levothyroxine	NR	Teja et al. [9]
<i>Article in French</i>					
<i>Article in Spanish</i>					
27/F	Diffuse non tender goitre, inc TSH, dec T4	DI, suprasellar mass	Suprasellar RT, vincristine, adriamycin, prednisolone, CCNU	Alive and well after 2 years	Demeocq et al. [10] Pastor Durán et al. [11]
1.5/M	MNG, (N) T4	DI, seborrhea, OM, airway obstruction	ST, prednisolone, 6-mercaptopurine, RT, DDAVP	Alive and well after 2.5 years	Lahey et al. [13]
27/M	Painless nodule right lobe of thyroid, inc TSH, dec T4, dec T3	DI, recurrent pneumothoraces, skin papules	Vinblastine, cyclophosphamide, prednisolone	NR	Sinisi et al. [14]
32/M	Thyroid nodule, (N) TSH, (N) T4, (N) T3	Submandibular salivary gland mass, gum, LCH otitis externa	Right hemithyroidectomy, vinblastine, prednisolone	No signs of active disease after 2 years	Green et al. [15]
16/M	Painful goitre, inc TSH, (N) T4	Suprasellar mass, DI, partial hypopituitarism, hepatomegaly	Desmopressin, hydrocortisone, prednisolone, cyclophosphamide, levothyroxine	NR	Gaines et al. [16]
31/F	Thyroid nodule, (N) TSH, (N) T4, papillary carcinoma concurrent with LCH	DI, mucosa, interstitial lung disease	Prednisolone, vincristine, methotrexate, chlorambucil, mucosal radiotherapy, TT, Iodine I31	NR	Golstein et al. [17]
36/F	Firm, 2 cm thyroid nodule, (N) TSH, (N) T4	Pathological lumbar compression fracture, DI, suprasellar mass	TT, spinal stabilisation, prednisolone, vinblastine, levothyroxine, oestrogen replacement, DDAVP	Alive 3 years later	Ho et al. [18]
16/M	Dec TSH, large goitre eventually causing airway obstruction	Panhypopituitarism, suprasellar hemangioblastoma	Desmopressin, hydrocortisone, levothyroxine, testosterone, ST	NR	Kirchgraber et al. [19]
10/M	Large goitre, (N) TSH, (N) T4	OM, seborrhea, Interstitial lung disease	Surgical resection, prednisolone	Died 12 years of age	Liu et al. [20]

Table 1 continued

Patient age (years)/gender	Clinical features and biochemical status of the thyroid gland	Other organ involvement	Treatment	Survival	Author
61/F	Thyroid nodule, inc TSH, dec T4, dec T3	DI	Near-total thyroidectomy, levothyroxine	NR	Maurea et al. [21]
40/F	Right lobe thyroid nodules	NR	Right hemithyroidectomy	Alive and well after 5 months	Tsang et al. [22]
19/F	Goitre	DI, hypothalamic mass, cystic pulmonary lesions	NR	NR	Chong [23]
58/M	Rubbery, diffusely enlarged goitre; dec RAI uptake, inc TSH, (N) FT4	DI, multiple bone lesions, Severe combined immunodeficiency	ST, RT, prednisolone, doxorubicin, desmopressin, levothyroxine	NR	Kitahama et al. [24]
27/F	Diffuse right lobe goitre, inc TSH, (N) T4	DI, lytic mandibular lesions, gum, skin, lung	NR	NR	Gomez-Plaza et al. [25]
61/F	Diffuse goitre, (N) thyroid function	Skin rash, splenomegaly	ST	NR	Orabona et al. [26]
32/M	Thyroid nodule, (N) TSH, (N) T4	Nil	Hemithyroidectomy	No evidence of recurrence after 4 years	Thompson [27]
37/F	Diffuse, slowly enlarging goitre	Nil	Hemithyroidectomy	No evidence of recurrence after 9 years	Thompson et al. [28]
55/F	Diffuse goitre, (N) TSH, (N) T4	Nil	Hemithyroidectomy	No evidence of recurrence after 9 years	Thompson et al. [28]
38/F	Thyroid nodule	Nil	Hemithyroidectomy	No evidence of recurrence after 3 years	Thompson et al. [28]
20/M	Diffuse goitre	Heart, lung, bone, skin, lymph nodes	NR	Death	Thompson et al. [28]
2/M	Diffuse goitre	Lung	NR	Death	Thompson et al. [28]
52/F	Thyroid involvement found at necropsy	Skin, bowel, liver, bone, lymph nodes	NR	Death	Thompson et al. [28]
28/F	Diffuse goitre	Gingival swelling	TT	Gingival involvement starting 1 year after thyroidectomy	Wang et al. [29]
28/F	Goitre, (N) TSH, (N) T4	Amenorrhoea	ST	NR	Coode et al. [30]
2.5/M	Firm goitre, inc TSH, (N) T4, (N). RAI uptake	Seborrhoea, progressive global neurological deterioration	Levothyroxine	Died at 5 yrs of age	Diamond et al. [31]
13/F	Firm 5 cm thyroid nodule, (N) hormonal profile	Nil	Excisional biopsy, prednisolone and vinblastine	NR	Sahoo et al. [32]
23/F	3 cm firm thyroid nodule	Nil	ST	NR	Dey et al. [33]

Table 1 continued

Patient age (years)/gender	Clinical features and biochemical status of the thyroid gland	Other organ involvement	Treatment	Survival	Author
43/F	4 cm painless thyroid nodule, (N) T4, (N) T3	Nil	Right hemithyroidectomy	Symptom free at 2 yrs	Saiz et al. [34]
43/M	2 cm thyroid nodule, (N) thyroid function tests, incidental 0.3 cm papillary carcinoma found at thyroidectomy	Nil	Left hemithyroidectomy	Symptom free at 2 yrs	Saiz et al. [34]
28/F	Goitre	DI, kidneys	Thyroidectomy	NR	el-Halabi et al. [35]
19/F	Diffusely enlarged goitre causing airway obstruction, inc TSH, dec T4	DI, hypogonadism, parathyroid infiltration	TT, dexamethasone, vincristine	Alive 5 yrs after	Yap et al. [36]
57/M	Two, firm 2 cm thyroid nodules; (N) TSH	Seborrhoea	ST, RT to skin lesions and thyroid bed	Alive and well 12 months later	Behrens et al. [3]
31/M	2 cm thyroid nodule, (N) TSH, (N) T4	Nil	Right thyroid lobectomy	Alive and well 3 months later	Behrens et al. [3]
<i>Article in French</i>					
25/F	TSH 1.9, FT4 4.4, FT4 4.4. Diffuse and firm 40 g enlarged thyroid	DI, lung, liver	Vinblastine, prednisolone, desmopressin, cyclosporine, levothyroxine, trimethoprim-sulfamethoxazole	NR	Mrad et al. [37]. Sampathkumar et al. [38]
42/F	Small left thyroid nodule	Nil	ST	Symptom free at 14 mo	Foulet-Roge et al. [39]
10/M	Fixed mass right lobe	Lung	Pulmonary wedge resection	Died at 1.5 year from respiratory failure	Chern et al. [40]
30/F	Right and left lobe mass. TFTs (N)	Nil	Near TT	NR	Zhu et al. [41]
<i>Article in French</i>					
45/F	Diffusely enlarged	Nil	ST (mediastinal portion)	NR	Khiri et al. [42]
29/M	Diffusely enlarged, inc. Antithyroid Abs	Skin, adjacent neck muscles, T8 vertebral body, Mastoid bone	TT with partial resection of oesophageal wall. Cladribine	NR	Elliott et al. [43]
46/F	Asymmetrically enlarged goitre. TFTs (N). Thyroglobulin level inc at 9,235 µg/ml	Nil	Attempted thyroidectomy aborted (sig. Hge), INF-α, Cladribine, Pentostatin	Partial remission, continued response 6 mo later	Braiteh et al. [44]
<i>Article in French</i>					
<i>Article in Polish</i>					
10 months/M	Goitre. T4 7.3, T3 12.4.	Lung, skin	Prednisolone, 6-mercaptopurine, methotrexate. TT	NR	Oudidi et al. [45] Kamińska et al. (Polish) [46] Cales et al. [47] Burnett et al. [48]
<i>Article in French</i>					
<i>Article in Chinese</i>					
					Oudidi et al. [49] Ma et al. [50]

Table 1 continued

Patient age (years)/gender	Clinical features and biochemical status of the thyroid gland	Other organ involvement	Treatment	Survival	Author
5 month/F	Soft tissue mass infraglottic space at level of thyroid. TFTs (N)	Skeletal muscle	ST, Prednisolone, vincristine, 6-mercaptopurine	Well at 18 mo	Hung et al. [51]
9/M	Goitre, TFTs (N)	Mastoid	ST, vinblastine, prednisolone	3 yr remission	Yağci et al. [52]
13/F	Multinodular goitre, TFTs (N), antithyroglobulin inc 1.086, antimicrosomal Abs inc 12.8	NR	ST, vinblastine, prednisolone	8 yr remission	Yağci et al. [52]
43/F	Thyroid enlargement, left lobe hard nodule. TSH (N)	NR	Left lobectomy	NR	Giovannella et al. [53]
53/F	Firm thyroid mass. Thyroid microsomal Ab 1331, inc TSH, dec T4.	Hypothalamus	ST	Well at 3 yrs	Deepak et al. [54]
55/F	Diffuse enlarged firm goitre	NR but concurrence with MALT of thyroid	Elective thyroidectomy	Symptom free at 3 mo	Licci et al. [55]
31/F	Enlarged diffusely firm nodular thyroid gland. TFTs (N), Autoimmune Abs neg, antithyroglobulin Abs pos	NR	TT	NR	Lollar et al. [2]
40/F	Enlarged thyroid with 2 nodules. TFTs N.	NR	Thyroidectomy	Died 3 days post op due to post op complications	Ramadas et al. [56]
26/F	Goitre. TSH 0.01, T3 11.4, T4 2.8, TRAb 61%	Nil	Thyroidectomy	Well at 3 yrs	Lassalle et al. [57]
28/M	Diffuse enlargement. Inc TSH 3.5, Dec T4 10.2, Antithyroglobulin >3,000	Left mastoid and petrous bone, Hypothalamus, Left musculus longissimus	Prednisolone, vinblastine, 6-mercaptopurine	NR	Wohlschlaeger et al. [58]
24/M	Enlarging goitre	Pleura, lung, SCM muscle	TT, Iodine 131, etoposide, dexamethasone	Stable, duration of follow up not specified	Jamaati et al. [59]
13/F	Diffuse goitre. TSH 10.32, T3 2.0, FT4 dec 0.8, Antithyroglobulin 154, Antithyroid peroxidase 36, Anti TH receptor neg.	Hypothalamus, parotid gland, external acoustic meatus, cervical lymph node, thymus	Vincristine, cytosine arabinoside, prednisolone	5 yr remission but dependent on insulin	Shima et al. [60]
21/M	Diffuse enlarged goitre. T4 dec 0.66, Antithyroid Abs neg.	Lung nodules	NR	NR	Uchiyama et al. [61]
3/M	Enlargement of both thyroid lobes. T4 7.74, T3 3.4.	Lung nodules	Prednisolone, vinblastine, 6-mercaptopurine	No recurrence at 1 yr	Lin et al. [62]
38/F	Goitre and nodule both lobes. Hypothyroid	Lung nodules, hepatomegaly	TT	Follow up discontinued by patient	Garcia Gallo et al. [63]
23/M	Thyroid mass. Subclinical hypothyroidism.	Hypothalamus	TT. Prednisolone and vinblastine.	Well at follow up. duration not specified.	Garcia Gallo et al. [63]
29/M	Neck mass	Oropharynx	Prednisolone, vinblastine, cladribine, imatinib	Death from acute pulmonary distress	Vergez et al. [64]

Table 1 continued

Patient age (years)/gender	Clinical features and biochemical status of the thyroid gland	Other organ involvement	Treatment	Survival	Author
5/F	Primary hypothyroidism. No clinical features. TSH > 60, T4 1.28.	NR	Vinblastine, prednisolone	Died at 2 mo of unknown cause, no post-mortem	Priyambada et al. [65]
52/F	Enlarged, diffusely firm thyroid. TSH 3.99, T4 7.2, T3 109	Nil	Right hemithyroidectomy	Well at 1 yr	Vilallonga et al. [66]
48/F	Hypothyroidism, on levothyroxine replacement therapy. Left sided thyroid swelling. FNA suggestive of medullary carcinoma. Dec TSH, (N)/T4	Nil	Left thyroid lobectomy	Well at 7 mo	Present case

M Male, F female, TT total thyroidectomy, ST subtotal thyroidectomy, DI diabetes insipidus, OM otitis media, RAI radioactive iodine, RT radiotherapy, nl normal, mo month(s), yr Year(s), dec decreased, inc increased, neg negative, pos positive, N normal, NR not reported, TSH thyroid stimulating hormone, T4 thyroxine, T3 triiodothyronine, Nil reported no additional organ involvement, Hge haemorrhage, INF interferon

suggested an epithelial neoplasm, with heavy eosinophilic infiltration, for which immunohistochemistry was negative for epithelial markers. Two months later, a second USS of the neck with FNA of the left thyroid lobe was performed which suggested medullary carcinoma.

Blood tests revealed a normal full blood count, electrolytes, urea, creatinine, calcium, and phosphate levels. Thyroid function tests reported a thyroid stimulating hormone (TSH) level <0.01 μL , Free T₄ of 15.7 pmol/L, and Free T₃ of 6.0 pmol/L (in keeping with treated hypothyroidism). In addition, serum calcitonin was recorded at <1.0 (normal range < 11.8 ng/L) and urine catecholamine levels were within normal range.

Following discussion of the case at a multidisciplinary team meeting, a diagnostic left hemithyroidectomy was performed 2 months later. The left lobe of the thyroid appeared macroscopically abnormal and enlarged due to the infiltrating tumour, which extended to the region of the left recurrent laryngeal nerve (Fig. 1). Due to the fact that there was no pre-operative diagnosis, and the left recurrent laryngeal nerve was not stimulating normally at 1 mA post left thyroid lobectomy, it was decided that the right thyroid lobe would not be removed at this stage.

Histologic examination revealed that the left thyroid lobe (12 g, and 4.5 × 3.5 × 2.0 cm) contained a circumscribed nodule composed of sheets and groups of round to ovoid cells with granular cytoplasm and vesicular grooved nuclei with numerous eosinophils (Fig. 2a–d). Areas of lymphocytic infiltrate were also noted. The ovoid tumour cells were positive for CD1a, S-100 protein, and CD68 (KP1), but were negative for CAM5.2, TTF-1, CD38, and CD20.

All of the above findings are in keeping with LCH of the thyroid gland.

The patient made a good recovery and within 2 months following hospital discharge underwent a computer tomography (CT) scan of the neck, thorax, abdomen, and pelvis, which did not reveal any suspicious lesions. The patient remains disease-free at last follow-up 9 months later and is currently under close clinical surveillance.

Materials and Methods for Literature Review

The literature review was performed using the Pubmed database from 1961 to 2011. The term “thyroid” and keywords which have been referred to as LCH (e.g., 1. “Histiocytosis X”, 2. “Eosinophilic granuloma”, 3. “Hand-Schuller-Christain disease”, 4. “Letterer-Siwe disease”, 5. “Langerhans cell (eosinophilic) granulomatosis”, 6. “Type II histiocytosis”, 7. Hashimoto-Pritzker disease, 8. “Self-healing histiocytosis”, 9. “Pure cutaneous histiocytosis”, 10. “Non-lipid reticuloendotheliosis”), were used

Fig. 1 The thyroid bed after removal of the left thyroid lobe. The left recurrent laryngeal nerve can be seen surrounded by tumour prior to its laryngeal entry

as part of the literature search. Seventy-five cases of LCH of the thyroid gland involving adults and children were identified (summarised in Table 1) of which 10 cases were written in a foreign language. Therefore, 65 English written cases (47 adult and 18 pediatric) of LCH of the thyroid gland were found in the medical literature.

Discussion

LCH lesions, first described in 1893, are composed of large histiocytes with abundant cytoplasm intermixed with lymphocytes and eosinophils [3, 67]. LCH may present as a tumour, skin rash, lytic bone lesions, pneumothorax, interstitial lung disease, central DI, or present with multiple affected organ systems within the human body [3]. Although posterior pituitary involvement is a common endocrinological presentation of LCH, manifestations of hypothalamic/pituitary axis disturbance and anterior pituitary deficiency, resulting in secondary or tertiary hypothyroidism, is less common [68].

LCH encompassed a group of conditions characterised by pathologic tissue infiltration with Langerhans cell granulomas [69].

Langerhan cells (LCs), characterised by cytoplasmic rod-shaped organelles (Birbeck granules), are a type of dendritic cell and are classed as antigen presenting cells of the skin epidermis [70]. LCs express surface glycoproteins such as CD1a and Langerin (CD207), which are both related to the major histocompatibility complex Class 1 and 2. Following antigenic activation, LCs migrate to lymph

Fig. 2 Photomicrographs of **a** a low power image showing an inflammatory infiltrate composed of histiocytoid (Langerhans) cells, lymphocytes, and eosinophils located between and separating the thyroid follicles (H&E $\times 10$); **b** the clusters of histiocytoid (Langerhans) cells are accompanied by lymphocytes and an occasional eosinophil located between thyroid follicles (H&E $\times 20$); **c** the

nuclear morphology exhibited by the histiocytoid (Langerhans) cells, which have relatively uniform ovoid vesicular nuclei with occasional grooves and granular cytoplasm (H&E $\times 40$), **d** histiocytoid (Langerhans) cells highlighted by CD1a immunostain, showing cytoplasmic staining. The adjacent thyroid follicular epithelial cells (right) are negative ($\times 20$)

Table 2 Showing demographics, clinicopathologic features, treatment and outcome of patients with LCH involving the thyroid gland

Patient demographics and clinicopathologic features	
Number of patients	66
Median age (years)	28
Male: female ratio	1:1.4
Goitre	59% (39/66)
Thyroid nodule(s)	25.8% (17/66)
Other (mass/non-diffuse swelling)	13.6% (9/66)
Thyroid swelling not reported	1.5% (1/66)
Thyroid profile	
Euthyroid	40.9% (27/66)
Hypothyroid	19.7% (13/66)
Hyperthyroid	0% (0/66)
Subclinical hypothyroidism	10.6% (7/66)
Subclinical hyperthyroidism	1.5% (1/66)
Not reported	27.3% (18/66)
Other	
Evidence of Hashimoto's thyroiditis	7.8% (5/66)
Treatment rate in children (n = 19)	
Surgery	5.3% (1/19)
Chemotherapy/radiotherapy only	26.3% (5/19)
Surgery + chemotherapy/radiotherapy	52.6% (10/19)
Other (levothyroxine)	5.3% (1/19)
Not reported	10.5% (2/19)
Treatment rate in adults (n = 47)	
Surgery	57.5% (27/47)
Chemotherapy/radiotherapy only	12.8% (6/47)
Surgery + chemotherapy/radiotherapy	21.3% (10/47)
Not reported	8.5% (4/47)
Combined treatment rate (n = 66)	
Surgery	42.4% (28/66)
Chemotherapy/radiotherapy only	18.2% (12/66)
Surgery + chemotherapy/radiotherapy	30.3% (20/66)
Not reported	9.1% (6/66)
Outcome	
No evidence of tumour	36.4% (24/66)
Alive with tumour	3.0% (2/66%)
Death from tumour	10.6% (7/66)
Death from other cause	3.0% (2/66)
Death from unknown cause	1.5% (1/66)
Disease free follow up (months/years)	3 months–9 years
Follow up not reported	45.5% (30/66)

Data based on the 66 reported English cases including present case and percentages corrected to one decimal place

nodes where naïve T-cells are stimulated to secrete various cytokines such as granulocyte–macrophage stimulating factor (GM-CSF), interleukin-15 (IL-15), tumour necrosis factor- α (TNF- α), and tissue growth factor-beta (TGF- β) for successful mounting of an immune response to the antigen in question [71].

LCH cells are similar to LCs in that they possess Birbeck granules, microscopically, but differ in their shape; LCH cells are more rounded and lack dendritic extensions. At a molecular level, LCH cells express CD1a, Langerin (CD207), and S-100 protein, but do not express markers which are possessed by mature dendritic cells, such as CD83 [71].

Although LCH has been considered to be a reactive process due to the lesions being composed of a mixture of eosinophils and lymphocytes with histiocytes, the latter cell type also exhibits monoclonality, which confirms that LCH is a neoplastic condition [72, 73].

Solitary thyroid gland involvement with LCH is extremely rare with most cases presenting as part of multisystem disease (Table 1) [66]. Therefore, the frequency of solitary thyroid gland involvement is difficult to assess owing to the very few cases documented in medical literature. However, adults tend to be affected in greater numbers than children when assessing thyroid involvement of LCH (47 adult vs. 18 pediatric cases) (Table 1). Females have shown to be slightly more affected than males by a ratio of 1.4:1, respectively (Table 2).

LCH cases involving the thyroid gland present with diffuse (59%) or nodular thyroid (25.8%) enlargement (Table 2). Thyroidal pain and obstructive symptoms secondary to a primary LCH goitre are rare [3]. In this case, the patient, who presented with a left-sided thyroid swelling, was experiencing dysphonia and globus symptoms owing to the infiltrative and compressive nature of the LCH tumour. A review of the literature has shown that thyroid hormone status in LCH involving the thyroid gland, may be variable, with cases being euthyroid (40.9%), hypothyroid (19.7%), and less commonly, subclinical hypothyroidism or hyperthyroidism (10.6% vs. 1.5%, respectively) (Table 2). In addition, antibodies such as antithyroglobulin and antimicrosomal antibodies have also been detected in cases of LCH involving the thyroid (Table 1). Furthermore, 7.8% of cases show evidence of lymphocytic (Hashimoto's) thyroiditis. LCH involving the thyroid gland has been confused with many common entities, such as undifferentiated carcinoma, lymphoma, lymphocytic thyroiditis, chronic granulomatous thyroiditis, and cystic degeneration of multinodular goitre [3]. Therefore, considering primary thyroid LCH as a differential diagnosis is difficult owing to the variable clinical presentation of this condition.

Initial steps in the diagnosis of primary thyroid LCH involve investigations into the work-up of thyromegaly, namely, neck USS and FNA. Although FNA cytology may be useful in the diagnosis for thyroid LCH [19, 33], this has shown to be variable with some cases being misdiagnosed as “atypical follicular epithelial cells” (as occurred in this case after the first FNA), and papillary or medullary carcinoma (as suggested in the second FNA performed in this

case) [3]. Therefore, histology remains the most sensitive diagnostic modality, although there have been cases of histological misinterpretation of LCH (interpreted as poorly-differentiated carcinoma) [29, 30]. Once primary thyroid LCH has been diagnosed, it has been suggested that further investigations such as CT, bone scintigraphy, and abdominal USS may be performed to determine multisystem involvement [51]. The patient in this case underwent a whole body CT which was negative for suspicious lesions suggesting any extra-thyroidal manifestation of LCH.

Treatment of choice for primary thyroid LCH is surgical resection by hemi-, subtotal, or total thyroidectomy [3, 51]. Of the 66 patients reviewed, 28 (42.4%) received surgery for thyroid involvement, 20 (30.3%) received surgery and adjuvant chemo-radiotherapy, and 12 (18.2%) received chemo-radiotherapy only (Table 2). At present, there is no evidence to concretely demonstrate improved outcome with adjuvant chemo-radiotherapy for primary thyroid LCH post-surgical resection. However, bony and soft tissue disease with LCH have shown an 88% and 69% control rate, respectively, with control rates being higher in children as compared to adults (100% vs. 79%) [74]. Chemotherapy regimens with agents such as glucocorticoids, vinblastine, etoposide, cyclophosphamide, cyclohexylchloroethylnitrosurea (CCNU), methotrexate, doxorubicin and 2-Chlordeoxyadenosine (2-CdA) have been tried in disseminated or aggressive disease [75, 76].

The overall mortality of LCH is 3%, compared with 15% in children [77]. When focussing on primary thyroid LCH, of the 66 cases reviewed, 24 (36.4%) reported no evidence of tumour post treatment (surgery $\pm$ chemo-radiotherapy) with disease-free followup ranging from 3 months to 9 years. Additionally, in 7 cases (10.6%) patients died of disease. Interestingly, 2 cases (3%) were reported to be alive with disease. In 30 cases (45.5%), follow-up was not reported.

From our literature review, the majority of children had a combination of surgery and chemotherapy for treatment of thyroid LCH (52.6%), whereas the majority of adults had surgery alone (57.5%), followed by surgery and chemotherapy or radiotherapy (21.3%) (Table 2).

Conclusion

LCH is a rare disease, especially when the primary tumour originates from the thyroid gland. The mainstay of diagnosis of this rare condition is through histological analysis and immunohistochemical staining (S-100 protein, CD1a, Langerin). This article also highlights the variability of results obtained by FNA of the thyroid gland which may be misleading in the pre-operative diagnostic stages of LCH of the thyroid gland. Furthermore, the use of additional

investigations, such as whole body CT, bone scintigraphy, and abdominal ultrasound, should be integrated within the investigative work-up protocol when LCH of the thyroid gland is diagnosed; this will allow for thorough investigation of extra-thyroidal LCH involvement. Although considered an inflammatory process, LCH is currently regarded as a low-grade malignancy and treatment remains mainly through local surgical resection with little evidence to suggest that adjuvant chemo-radiotherapy post thyroid resection provides a better outcome. Therefore, due to the lack of peer-reviewed articles on a treatment regimen for LCH of the thyroid gland, along with prolonged follow-up periods, studies assessing adjuvant and neo-adjuvant chemo-radiotherapy with local surgical resection with disease outcome data analysis are highly recommended.

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