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Localized Erdheim-Chester disease involving the thyroid gland—a case report

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Abstract

Background: Erdheim-Chester disease (ECD) is a rare multisystemic histiocytic disorder of unknown etiology. Isolated neck involvement has not been reported in literature.

Case presentation: An elderly male presented to our outpatient department with neck swelling of 1-month duration. Contrast-enhanced CT scan of the neck showed a mass involving the left thyroid/perithyroidal tissue with encirclement of the common carotid artery. Tru-Cut biopsy with immunohistochemistry showed CD68+, CD1a- histiocytic infiltrates with Touton giant cells compatible with ECD. *BRAF*^{V600E} mutation came out to be positive. PET-CT did not reveal involvement of any other body organs. After counseling for further treatment options, the patient chose to follow up without any active treatment. The disease has not progressed at a follow-up of 1 year.

Conclusion: We present a case of ECD involving the thyroid gland in isolation. Absence of other organ involvement should not deter the treating physician from considering the possibility of ECD. Immunohistochemistry and testing for *BRAF*^{V600E} mutation are important from the diagnostic as well as potential therapeutic point of view.

Keywords: Erdheim-Chester disease, Non-Langerhans cell histiocytosis, Thyroid gland, Immunohistochemistry, Case report

Background

Erdheim-Chester disease (ECD) is an idiopathic rare systemic disorder characterized by clonal proliferation of myeloid progenitor cells, presenting as an osteosclerotic lesion involving long bones with or without extraskeletal tissue involvement. Previously considered as non-Langerhans cell histiocytosis (non-LCH), ECD has been recently categorized along with LCH as a subgroup of "histiocytosis of 'L' type" in view of molecular and genetic similarities between the two and coexistence of the two pathologies in up to 20% of cases [1, 2].

The consensus-based diagnostic criteria of ECD (Veyssier-Belot and Haroche criteria) require the fulfillment of the following parameters [3]:

1. Histopathologic evidence of xanthogranulomatosis, foamy macrophages, and polymorphic granulomas intermixed with fibrosis, and immunohistochemistry showing CD 68+ and CD 1a- histiocytes
2. Skeletal involvement with bilateral symmetrical osteosclerosis of the cortex of the diaphyseal and metaphyseal regions of the long bones (more commonly lower limbs)

Though the disease is classically defined based on the above criteria, cases without skeletal involvement have been identified in literature on the basis of the classic xanthogranulomatous pathology and immunohistochemical staining pattern [3–6]. In fact, the disease without skeletal involvement is a distinct subset of ECD in the revised histiocytosis classification [2]. ECD presents with multiorgan involvement in the vast majority of the cases; however, isolated organ involvement has been reported [7].

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To date, around 750 cases of ECD have been reported in literature (including around 500 cases in English literature in a PubMed search) [8, 9]. Involvement of the extracranial head and neck region has been reported sparsely, with all of these cases being a part of systemic illness. To our knowledge, there is no report in literature describing ECD presenting with primary/isolated neck involvement. We report a case of ECD presenting as a nodulo-infiltrative lesion involving the thyroid gland and carotid sheath without systemic involvement. A pertinent review of literature is presented.

Case presentation

A 68-year-old male patient presented to our outpatient department with a history of anterior neck swelling for 1 month. The patient gave a history of intermittent low-grade fever lasting for around 3 weeks preceding the onset of the swelling. The etiology of the fever could not be discerned. Four to 5 days after the fever subsided, the patient developed the neck swelling, which was not painful and increased in size in the initial few days, stabilizing at the present size thereafter. There was no history of loss of appetite, weight loss, night sweats, and fatigue. The patient did not give a history suggestive of hyper/hypothyroidism. There was no history of change in voice and difficulty in swallowing or breathing. The patient did not have any comorbidities, and there was no history of any other visible body swelling.

On local examination, the swelling was around 4 ×3 cm in size and involved the left-side thyroid region and midline (Fig. 1). On palpation, the swelling was ill-defined, hard, non-pulsatile, non-tender, and without increased temperature of the overlying skin. It was adherent to the overlying skin and fixed to the deeper neck structures. There was slight movement of the swelling with deglutition but not with tongue protrusion. There were no other palpable neck swellings. Oral cavity, oropharyngeal and laryngeal examination findings were within normal limits. The patient was comfortable at rest with a normal voice, and the general systemic examination was normal. Blood tests showed anemia (Hb 9.1 g/dL; normal 13–17 g/dL), raised total leucocyte counts (12,490/μL; normal 4000–11,000/μL), and a raised erythrocyte sedimentation rate (71 mm in the 1st hour; normal range 0–14 mm in the 1st hour). The thyroid function tests were within normal limits.

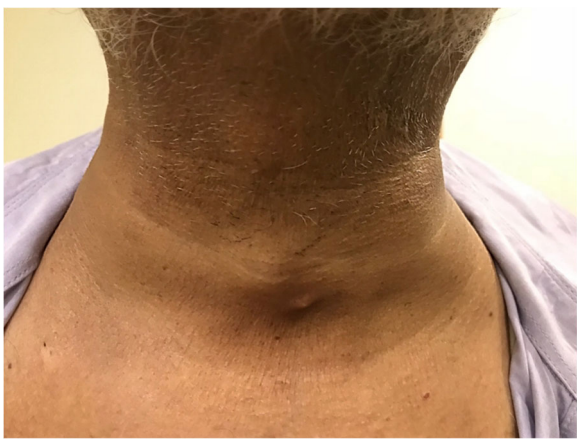

Fig. 1 Ill-defined anterior neck swelling involving midline and left side of the neck

A contrast-enhanced computed tomography (CECT) of the neck and chest was obtained which showed an ~ 5 × 3.5 × 3.7 cm enhancing plaque-like soft tissue lesion with areas of necrosis seen in the left side of the lower neck involving the strap muscles, sternocleidomastoid muscle, and left lobe of the thyroid gland (Fig. 2a). The lesion was engulfing the internal jugular vein (IJV) (which was not defined in the lower neck) and the common carotid and internal carotid artery (ICA) (Fig. 2b). The lumen of the carotid artery was patent. There was no significant cervical or mediastinal lymphadenopathy or any significant finding in the chest CT scan. Keeping in mind a possibility of anaplastic carcinoma of the thyroid, a core biopsy using an 18-gauge core biopsy needle was obtained under ultrasound guidance from the swelling, and the specimen was sent for histopathology as well as Ziehl-Neelsen (Z-N) staining and GeneXpert MTB/RIF assay (Xpert) (Cepheid, Sunnyvale, CA). The Z-N stain, culture, and GeneXpert did not reveal any positive findings. The histopathology showed skeletal muscle and fibroadipose tissue infiltrated by sheets of foamy histiocytes and multinucleate Touton-type giant cells along with lymphoid cells (Fig. 3a). There was no evidence of increase in eosinophils/definite granuloma/necrosis/caseous necrosis/definitive emperipolesis/viral inclusions or fungal hyphae. Immunohistochemistry showed strong positivity for CD68 (Fig. 3b), while CD1a (Fig. 3c) and S-100 (Fig. 3d) were negative. Additionally, the stains for CD3 and CD20 were positive, while those for CD30, CK, and ALK-1 were negative. The special stains for AFB and fungus (Grocott-Gomori's methenamine silver stain) were negative. The histopathology and immunohistochemistry picture was highly suggestive of Erdheim-Chester disease. An analysis of $BRAF^{V600E}$ (Ventana platform immunohistochemistry; Ventana Medical Systems, Tucson, AZ) was performed for diagnostic and therapeutic implications and came out to be positive (Fig. 3e). An ^{18}F-deoxyglucose positron emission tomography (FDG-PET) scan was performed, which showed no other focus of increased activity in the body (Fig. 2c). The patient was given the option of watchful waiting with the active treatment being offered if the disease progresses and upfront therapy with vemurafenib in view of symptomatic presentation of the disease;

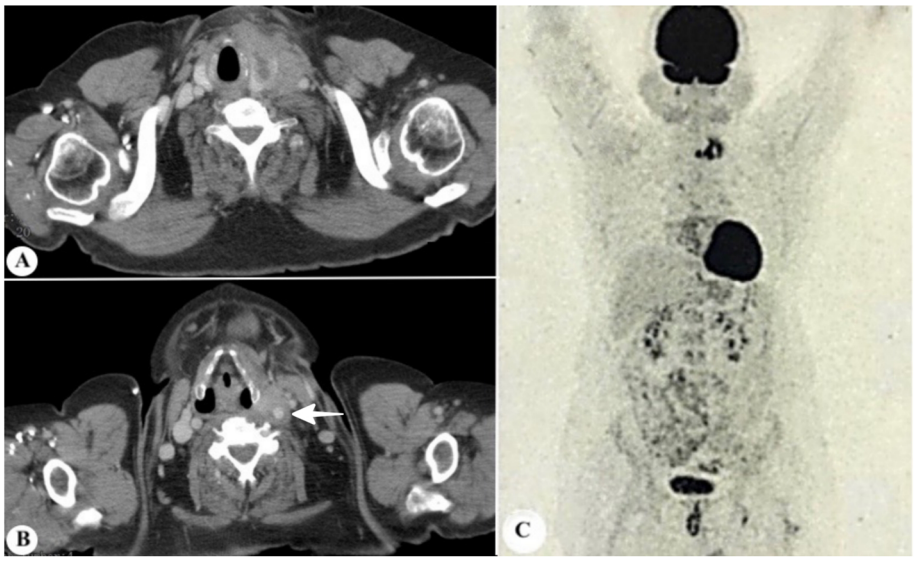

Fig. 2 **a**, **b** Contrast-enhanced CT scan of the neck, axial views, showing **a** mildly enhancing soft tissue involving the left lobe of the thyroid and adjacent strap muscles and **b** "pericarotid cuffing" of the common carotid and internal carotid artery (arrow) with the lesion. The internal jugular vein is not visualized because of compression by the mass lesion; however, there is no evidence of carotid stenosis. **c** Whole-body FDG-PET scan showing increased uptake in the left thyroid/perithyroid region (arrow) without any abnormal uptake elsewhere in the body

however, the patient opted for a watchful waiting. At a clinical follow-up of 1 year, there are no new symptoms and the local disease has not progressed.

Discussion

Though symmetrical diaphyseal/metaphyseal cortical osteosclerosis of the lower extremity long bones is typical of ECD, cases without bone involvement have been reported in literature [3–6], and the absence of bone involvement should not deter the clinician from considering this possibility. Moreover, bone involvement may not be the first manifestation of the disorder and may be asymptomatic in up to 50% of the patients [10]. Localized organ involvement has been reported in a

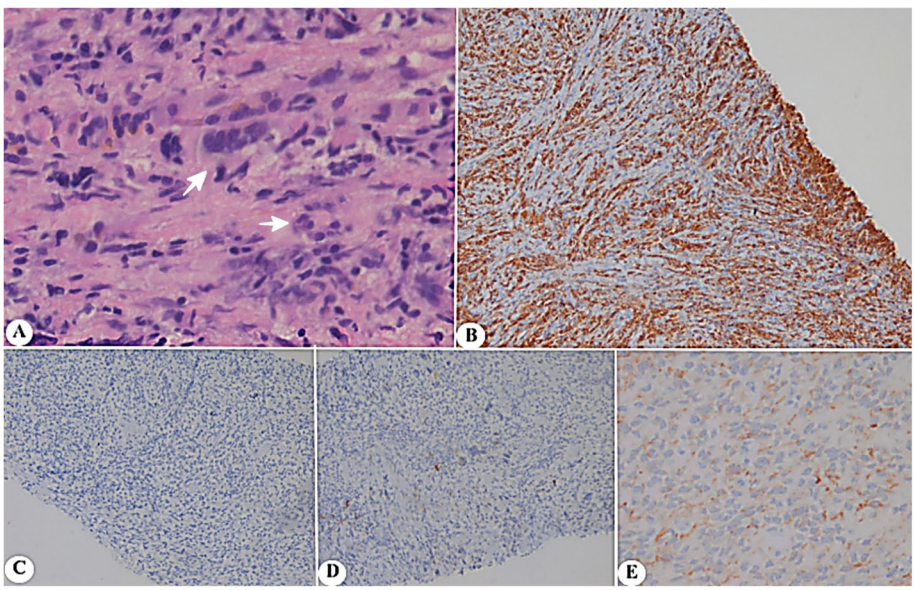

Fig. 3 **a** Histopathology of the Tru-Cut biopsy specimen from the lesion showing fibroadipose tissue infiltrated by the sheets of foamy histiocytes and Touton-type giant cells (arrows) along with lymphoid cells (hematoxylin and eosin stain; original magnification × 400). Immunohistochemistry showing **b** diffuse positive staining for CD68 (original magnification × 100), **c**, **d** negative staining for CD1a and S-100, respectively (original magnification × 100), and **e** positive staining for $BRAF^{V600E}$ mutation (Ventana platform immunohistochemistry; original magnification × 400)

patient with pulmonary parenchymal and mediastinal lymphadenopathy [7]. However, isolated thyroid and perithyroidal involvement has not been described to date. The atypical presentation without bone involvement in our patient shifted the attention away from the clinical possibility of LCH or ECD, which came as a surprise on immunohistochemistry, and the workup for systemic disease turned out to be negative.

Various disorders presenting with histiocytic infiltrates of tissue need to be differentiated from ECD. These disorders in general tend to present as tumefactive nodular or infiltrative lesions and present great diagnostic and management dilemma. The key to differentiate these disorders lies in characterizing the histopathological and immunopathologic profile. The other differentials on clinical evaluation in our patient were anaplastic carcinoma of the thyroid, lymphoma, tuberculosis involving the thyroid gland, sclerosing thyroiditis, and Rosai-Dorfman disease (Table 1). Histopathology was helpful in ruling out these differentials, while a definitive diagnosis of ECD was established by the typical immunohistochemistry picture.

Histopathologically, ECD is characterized by infiltration of the target tissue with sheets of foamy histiocytes and intermixed lymphoplasmacytic infiltrates and Touton-type giant cells (fusion of the foamy macrophages forming a ring of nuclei with central eosinophilic and peripheral foamy, vacuolated cytoplasm) in a background of variable surrounding fibrosis. The characteristic pattern of immunostaining (CD68+, CD163+, CD1a-, S100-) is central to differentiate ECD from other similar presenting disorders with underlying histiocytosis or lymphoplasmacytic infiltrates [11].

One of the characteristic imaging finding in ECD with vessel involvement is a “coated artery” appearing as perivascular cuffing without arterial stenosis. This finding is usually observed in the aorta with few cases being reported with involvement of the vertebral artery. Only one case of ECD with involvement of the carotid artery has been reported in literature [12]. Our patient had a typical appearance with a coated common/internal carotid artery without stenosis; the internal jugular vein was, however, compressed by the lesion and was not discernible.

Routine blood tests are usually normal in these patients, except ESR/CRP, which are commonly elevated. Once the diagnosis is made, further workup needs to focus on the systemic involvement and genetic analysis of the tissue biopsy specimen which may assist with targeted molecular therapy. Treatment is indicated for patients with [7]:

1. Symptomatic disease,
2. Evident/impending organ dysfunction, and
3. Central nervous system involvement (including asymptomatic patients).

A patient not conforming to the above indications may be kept under regular follow-up to monitor the disease, since the disease progression varies among individuals and there is no known cure.

The somatic mutations activating the mitogen-activated protein kinase (*MAPK*) signaling pathway have been identified in most of the patients with ECD and reinforce the neoplastic designation of the disorder. The commonest of these mutations involves the $BRAF^{V600E}$ locus, which has been described in around 70% of patients [13]. Targeted therapy with BRAF inhibitor vemurafenib/dabrafenib is promising in these patients and may be considered as first-line treatment. Apart from therapeutic considerations, the

Table 1 Differential diagnosis for the neck swelling in the present case

SN	Differential diagnosis	Differentiating features from ECD
1	LCH	1. IHC - S-100+ve 2. EM - Birbeck granules
2	Anaplastic carcinoma thyroid	Malignant infiltration of the thyroid gland
3	Lymphoma	Positivity for specific lymphoma IHC panel distinct from ECD
4	Sclerosing thyroiditis	1. Diffuse fibrosis 2. Absence of Touton giant cells
5	IgG4-related disease	High levels of tissue IgG4+ve plasma cells and IgG4+/IgG ratio
6	Tuberculosis	1. Caseating epithelioid granulomas 2. Absence of Touton-type giant cells
7	Sarcoidosis	Non-caseating epithelioid granulomas
8	RDD	1. Emperipolesis 2. CD68+, CD163+, S-100+, CD1a-

SN serial number, *ECD* Erdheim-Chester disease, *LCH* Langerhans cell histiocytosis, *IHC* immunohistochemistry, *EM* electron microscopy, *RDD* Rosai-Dorfman disease

identification of this mutation is important from a diagnostic point of view as well, for the cases difficult to distinguish from adult xanthogranulomatosis [2]. Our patient was found to be positive for $BRAF^{V600E}$ mutation, which further strengthened the diagnosis.

Other treatment options include INF-α (starting in a dose of 3 MU, 3 times/week and escalating to a maximum of 9 MU, given 3 times/week depending upon the response and tolerability of the patient) or the pegylated version, Peg INF-α (weekly dose of 135 μg, escalating to a maximum of 200 μg given weekly, depending on patient response and tolerability). INF-α has been traditionally the treatment of choice in the pre-BRAF inhibitor era and is still considered by some to be the first-line agent for treatment-naïve patients [3]. In patients not suitable or responding to the above agents, glucocorticoids, cytotoxic chemotherapeutic agents (cladribine, cyclophosphamide), imatinib, sirolimus, methotrexate, anakinra, infliximab, and MEK inhibitors have been used in various case reports with varying degrees of response [14]. The disease, in our patient, has been non-progressive without any evidence of organ dysfunction during a follow-up of 1year without any specific treatment.

Conclusion

ECD is typically a multisystem disease with involvement of the diaphyseal and metaphyseal cortex of the long bones of periphery. Isolated organ involvement is unusual, and to our knowledge, the current case is the first to present with localized thyroid/perithyroidal involvement. The natural history of this subcategory of disease is yet to be defined. The disease in our patient has not progressed over a course of 1 year.

Abbreviations

MTB/RIF: *Mycobacterium tuberculosis*/rifampicin; LCH: Langerhans cell histiocytosis; ECD: Erdheim-Chester disease; PET/CT: Positron emission tomography/computed tomography; INF-α: Interferon-alpha; MEK inhibitor: MAPK/ERK (Mitogen-activated protein kinase/extracellular signal-regulated kinase) kinase inhibitor

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Authors' contributions

The contribution of the authors to the script is as follows: AS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: AS, PG, MH, DG, ACH, and KKH. Acquisition, analysis, or interpretation of data: AS, PG, MH, DG, ACH, and KKH. Drafting of the manuscript: AS, PG, MH, DG, ACH, and KKH. Critical revision of the manuscript for important intellectual content: PG, MH, DG, ACH, and KKH. Administrative, technical, or material support: AS, PG, MH, DG, ACH, and KKH. The authors read and approved the final manuscript.

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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