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Langerhan Cell Histocytosis-A Review

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Abstract

Aim:
The current review article highlights the various mechanism of pathogenesis of langerhan cell histocytosis .

Objective:
Langerhan cell histiocytosis is a rare disease with a variable clinical presentation, and its diagnosis and treatment depend on the extent and severity of disease such as bone, pulmonary (lung), thyroid and orbit.

Background:
Langerhans cell histiocytosis (LCH) is a group of idiopathic disorders characterized by the presence of cells with characteristics similar to bone marrow–derived Langerhans cells juxtaposed against a backdrop of hematopoietic cells, including T-cells, macrophages, and eosinophils.

Reason:
As patients with Langerhans cell histiocytosis may have a higher-than-average risk of developing cancer later in life, including lymphoma and leukemia. The current review article provides further insight to the pathogenic mechanism and its complications .

INTRODUCTION:

Langerhans cell histiocytosis (LCH) is a rare neoplastic disease of antigen presenting cells. It is a proliferation of Langerhans cells that are intermixed with inflammatory cells, in particular eosinophils. Langerhans Cell Histocytosis (LCH) is a specific type of histocytic syndrome characterized by infiltration of tissues with a specific dendritic cell, the Langerhans cell [1]. Officially known as histocytosis X (or eosinophilic granuloma), but now it is evident that the "X" cells are Langerhans cells. Langerhans cell histiocytosis (LCH) is a systemic granulomatous disease of the dendritic system with a variable clinical course and may affect approximately any organ such as orbit, lung, thyroid gland etc. Orbital involvement is usually seen in patients with chronic lesions and exceptional in acute disseminated forms of LCH [2]. Pulmonary langerhan cell histiocytosis (PLCH) is a rare disease which occurs almost exclusively in smokers [3, 4]. LCH involving the thyroid gland, with variable diagnoses on fine needle aspiration (FNA) cytology. It also involves the skin or mucous membrane and bone marrow.

ORBITAL LANGERHAN CELL HISTIOCYTOSIS:

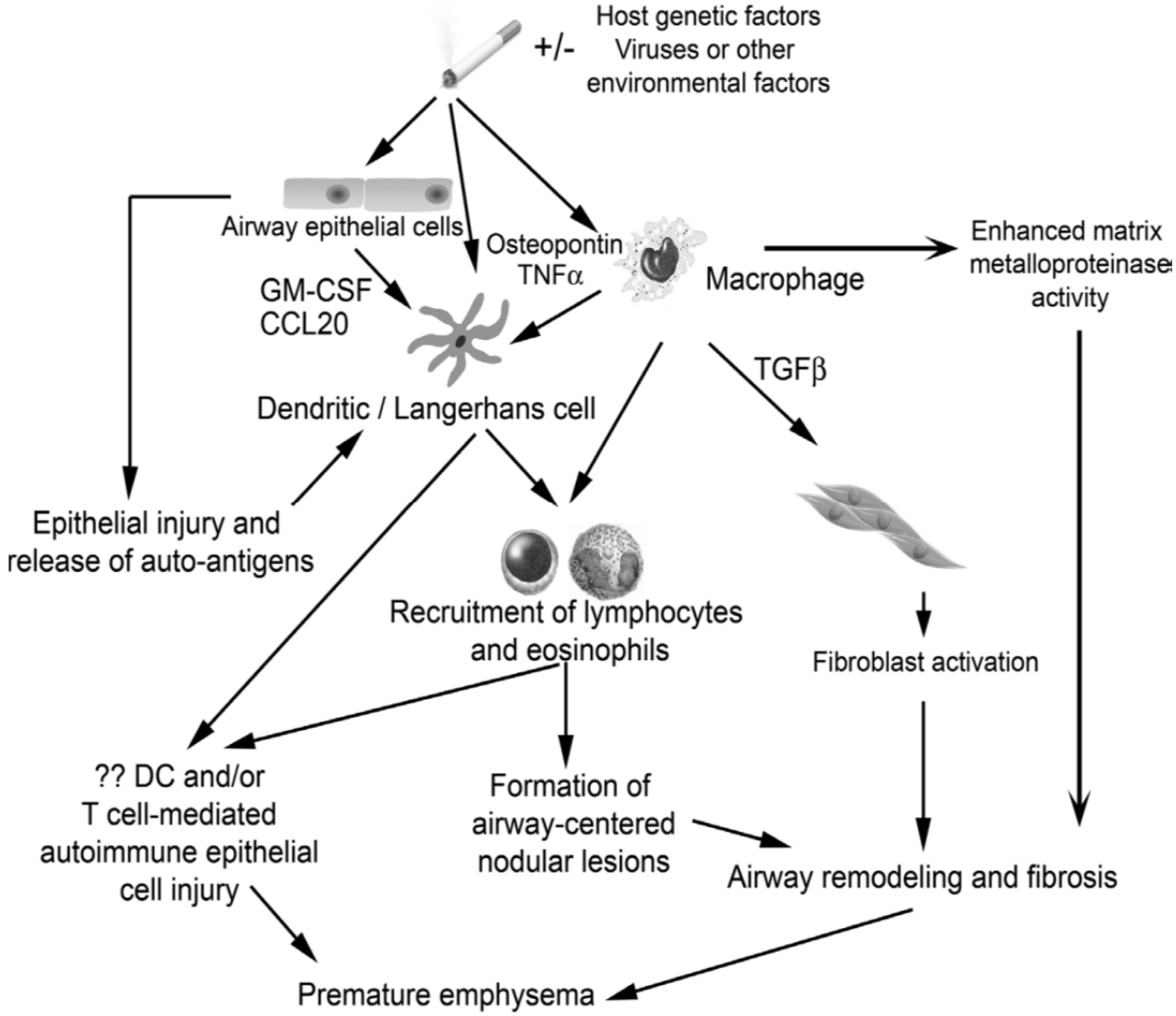
Langerhan cell histiocytosis represents a clonal proliferation of langerhan cells. Isolated orbital infiltrates are the most common manifestation of LCH of the ocular adnexa [5, 6]. LCH of the orbit usually presents as an isolated bone lesion with an associated soft tissue mass, although it can also be associated with multifocal or multisystemic disease [7, 8, 9, and 10]. It occurs predominantly in the superior or superolateral orbital roof and exhibits other features depending on the location of the Langerhans cell infiltrate such as a visible mass with ptosis and/or (erythematous) swelling if located in the anterior orbit. This may be misinterpreted as an infectious process.

Proptosis is predominantly seen in lesions that involve the posterior orbit. This may be accompanied by diabetes insipidus and skull lesions forming the triad formerly called Hand-Schüller-Christian disease. Depending on the location and the size of the lesion as well as the infiltrated structures such as extra ocular muscles ocular movement may be impaired resulting in diplopia and nerve palsies may occur. Visual acuity may be somewhat affected in young patients due to ptosis and the development of amblyopia.Fundus abnormalities such as optic disc edema, dilated venous channels, and macular edema, in eyes with orbital LCH [7]. Immunohistochemical markers that may be positive in LCH include adenosine triphosphatase, peanut lectin binding, alphamannosidase, CD207 (Langerin), and fascin. LCH is not unequivocally regarded as a true neoplasm and may represent an atypical immunoreaction.The severity of this disease is directly influenced by an immature aberrant immune system. Aberrant immune interaction between the clonal proliferation of dendritic cells and T cells leading to a "cytokine storm.Proliferation of cytokines leads to infections such as (EBV, CMV, HHV-6), genetic disorders, malignancies (medulloblastoma, retinoblastoma, medullary astrocytoma, glioma), and environmental influences have also been implicated in the pathogenesis of LCH [11, 12]. Histopathologically, the histiocytic infiltrate consists of lymphocytes, plasma cells, polymorphonuclear leukocytes, macrophages (histiocytes) and varying amount of necrosis can be also present . The lesions are very often vascular and erythrocytes are frequently observed due to hemorrhage

Mitotic figures (MF) are also occasionally found. Orbital involvement typically manifests as a solitary lesion that carries a favorable prognosis.

PULMONARY LANGERHAN CELL HISTIOCYTOSIS:

Pulmonary langerhan cell histiocytosis represent polyclonal proliferation of langerhan cell. PLCH is characterized by prominent peribronchial inflammatory changes , suggesting injury of small airways by an inhaled irritant such as cigarette smoke. Cigarette smoke induces inflammatory dendritic cell responses directly by activating inflammatory transcription factors. Cigarette smoke induces tumor necrosis factor-alpha (TNF alpha) production from epithelial cells and macrophages, which is a critical differentiation and activation factor for langerhans cells . Cigarette smoke also stimulates granulocyte macrophage colony stimulating factor (GM-CSF) by epithelial cells and fibroblasts [14]. An immunohistochemical study showed GM-CSF to be abundantly expressed in the epithelium of bronchioles affected by inflammatory PLCH lesions [15]. Cigarette smoke induces the production of transforming growth factor-beta (TGFb) by epithelial cells .TGF beta is an essential factor in the development of langerhans cells [16], and is an important cytokine involved in the process that leads to tissue remodelling by fibrosis and scar formation [17]. Cigarette smoke also induces the production of dendritic cell chemokines like chemokine (C-C motif) ligand 20 (CCL20 or Macrophage Inflammatory Protein-3 alpha), which is likely derived from an epithelial source [18]. It is highly plausible that smoking-induced production of TNFa, GM-CSF, TGFb and CCL20 by cells in the proximity of lung dendritic and langerhans cells results in sustained stimulation of dendritic and Langerhans cells and their precursors, facilitating their local expansion in peribronchiolar regions. Excessive recruitment of circulating monocytes (potentially directly induced by cigarette smoke) is likely to be an essential mechanism by which expansion of the dendritic and Langerhans cell pool occurs around small airways [19]. Histologically upper panel shows a low-power microscopic picture with nodular airway-centered lesions showing microcystic change (original magnification, hematoxylin and eosin stain). The lower panel shows diffuse infiltration of lung tissue with Langerhans cells showing vesicular nuclear chromatin, irregular nuclear contour and moderate amount of pale cytoplasm devoid of phagocytosed material. Many eosinophils are also intermixed among langerhans cells .



THYROID GLAND KANGERHAN CELL HISTIOCYTOSIS:

LCH rarely involves the thyroid gland. LCH is associated with the posterior pituitary, presenting as diabetes insipidus. LCH lesions, are composed of large histiocytes with abundant cytoplasm intermixed with lymphocytes and eosinophils [21, 22]. 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 [21]. Although posterior pituitary involvement is a common endocrinological presentation of LCH, manifestations of hypothalamic/pituitary axis and anterior pituitary deficiency, resulting in secondary or tertiary hypothyroidism. LCs expresses 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 migrates to lymph nodes. Microscopically, 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 [23]. LCH involving the thyroid gland has common entities, such as undifferentiated carcinoma, lymphoma, lymphocytic thyroiditis, chronic granulomatous thyroiditis, and cystic degeneration of multinodular goitre .T- cells are stimulated to secrete various cytokines such as granulocyte–macrophage stimulating factor (GM-CSF), interleukin-15 (IL-15), tumour necrosis factor-alpha (TNF-a), and tissue growth factor-beta (TGFb) for an immune response to the antigen .

DIAGNOSIS:

The clinical differential diagnosis of ophthalmic LCH includes periorbital cellulitis, acute dacryocystitis, (ruptured) dermoid cyst, hematoma, inflammatory pseudotumor, pilomatrixoma, leukemia, sarcoma, metastastic neuroblastoma, rhabdomyosarcoma, and other tumors. The histologic differential diagnosis of LCH include giant cell reparative granuloma, hemorrhagic cyst, cholesterol granuloma (cholesteatoma),Erdheim-Chester disease[24],giant cell aneurysma of bone, giant cell tumor, and histiocytic sarcoma. PLCH from other cystic lung diseases like lymphangioleiomyomatosis (LAM), Birt-Hogg- Dube syndrome, or emphysema . Dyspnea and unproductive cough are the most common symptoms [25, 26]. Constitutional symptoms, including fever, sweats and weight loss. Diagnosis of primary thyroid LCH involve thyromegaly. Although FNA cytology may be useful in the diagnosis for thyroid LCH [27, 28],

TREATMENT:

Incisional and excisional biopsies are preferred over fineneedle aspiration biopsy.Treatment includes curettage/excision in combination with intralesional steroids, radiation, chemotheraphy, bone marrow transplantation and immunotheraphy. Bronchoscopy and lung biopsy for pulmonary langerhan cell histocytosis.Thyroidectomy is a treatment of langerhan cell histiocytosis.

CONCLUSION :

LCH has a myriad of manifestations and multiple organ involvement.LCH can also lead to a wide array of other complications .Thus the current review highlights the most common manifestation and organs affected thus aids in prompt diagnoses and treatment.

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