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Editorial

Tinge and Percolate-Erdheim Chester Disease

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Erdheim Chester disease emerges as an exceptionally discerned, clonal disorder demonstrating infiltration of histiocytic cells within various tissues and frequent involvement of multiple organs. Initially scripted by William Chester and Jakob Erdheim in 1930, the condition is additionally designated as polyostotic sclerosing histiocytosis. The disorder was contemplated to be an inflammatory disease and carried a preceding nomenclature of lipoid (cholesterol) granulomatosis. With the current World Health Organization (WHO) classification of tumours of Haematopoietic and Lymphoid Tissues 2016, the disorder is categorized within 'L' group of revised histiocytic disorders classification.

A concordance of cogent clinical symptoms, histological features and radiographic findings appear pre-eminent for appropriate disease discernment. Systemic disease is commonly associated with lesions confined to bone, pulmonary parenchyma, central nervous system and retroperitoneum as hairy kidney or coated aorta.

Associated clinical symptoms and disease outcomes are contingent to site of disease occurrence. An estimated > 50% lesions depict BRAF V600E genetic mutations.

Erdheim Chester disease commonly occurs within 16 years to 80 years with median age of disease emergence at 57 years. The condition is exceptionally discerned within paediatric population or adolescents. A male predominance is observed with male to female proportion of 3:1 [1,2].

Majority (>95%) of subjects depict skeletal lesions which are especially confined to long bones of lower extremities. Extra-skeletal lesions (~60%) frequently arise within the retroperitoneum, renal parenchyma, cardiovascular system or pulmonary parenchyma. Up to 30% instances delineate lesions confined to central nervous system and pituitary gland.

Cutaneous disease appears in ~25% subjects whereas orbit and testis are infrequently involved [1,2].

Erdheim Chester disease depicts activating mutations within mitogen activated kinase (MAPK) pathway with consequent accumulation of histiocytic cells within the tissue and enhanced expression of cytokines. An estimated >90% neoplasms depict genomic mutations within mitogen activated protein kinase (MAPK) pathway. Commonly, chromosomal mutations within BRAF V600E gene appears in >50% lesions.

Additionally, somatic mutations within MAP2K1, ARAF, MAP2K2, KRAS and NRAS are exemplified [2,3].

Subjects with Erdheim Chester disease demonstrate inflammatory cytokines with augmented serum levels of interferon alpha (IFNα), interleukin 12 (IL12) or monocyte chemotactic protein1 along with decimated levels of interleukins 4 and 7 (IL4 and IL7), a phenomenon which indicates initiation of Th-1-mediated systemic immune response. Erdheim Chester disease delineates enhanced prevalence of clonal myeloid neoplasms, indicative of occurrence of a clonal hematopoietic precursor [2,3].

Clinically, the condition is associated with heterogeneous clinical course and may represent as an asymptomatic disorder or a progressive, lethal disease. Distal extremities may represent with bone pain on account of skeletal involvement [2,3].

Commonly asymptomatic, cardiovascular disease is appropriately discerned upon adoption of cogent imaging techniques.

Retroperitoneal fibrosis may concur with bilateral hydronephrosis wherein pelvic ureters and inferior vena cava may be excluded from the lesion [3,4].

Pulmonary lesions are frequently asymptomatic although cough or dyspnoea may occur [3,4].

Erdheim Chester disease confined to pituitary gland may represent with central diabetes insipidus which may arise within a decade preceding the condition [3,4].

Central nervous system lesions preponderantly manifest with cerebellar and pyramidal syndromes [3,4].

Cutaneous variant represents with periorbital, xanthelasma-like lesions wherein orbital disease may induce pain, blindness, exophthalmos and oculomotor nerve dysfunction [3,4].

Upon microscopy, characteristic and significant infiltration of soft tissue with bland histiocytic cells or foamy macrophages impregnated with xanthomatous cytoplasm is encountered. Aforesaid macrophages are admixed with few lymphoid cells and plasma cells wherein the cellular infiltrate is circumscribed by fibrotic tissue. Touton giant cells are frequent [4,5].

Erdheim Chester disease may configure as a component of mixed histiocytosis, Langerhans cell histiocytosis or Rosai-Dorfman disease [4,5].

Staging of bone tumours confined to appendicular skeleton, trunk, skull and facial bones (American Joint Committee on Cancer 8th edition) [4,5]:

- Stage IA: T1, N0, M0, G1-GX.
- Stage IB: T2-3, N0, M0, G1-GX.
- Stage IIA: T1, N0, M0, G2-G3.
- Stage IIB: T2, N0, M0, G2-G3.
- Stage III: T3, N0, M0, G2-G3.
- Stage IVA: Any T, N0, M1a, any G.
- Stage IVB: Any T, N1, any M, any G OR any T, any N, M1b, any G.

Erdheim Chester disease appears immune reactive to histiocytic markers as CD14, CD68, CD163 and demonstrates diffuse, intense staining with Factor XIIIa. Nearly 50% lesions appear immune reactive to BRAF V600E [4,5].

Tumour cells appear immune non reactive to CD1a, Langerin, S100 protein, actin, desmin, epithelial membrane antigen (EMA), cytokeratin AE1/AE3 or CAM5.2. Besides, immune non reactivity to CD31, CD34, Melan A and human melanoma black 45 (HMB45) antigen is expounded [4,5].

Erdheim Chester disease requires segregation from neoplasms as reactive histiocytic proliferations, Langerhans cell histiocytosis, juvenile xanthogranuloma or Rosai Dorfman disease [5,6].

Erdheim Chester disease may be appropriately ascertained by concurrence of cogent clinical symptoms, radiographic images, histopathological features and molecular manifestations [5,6].

Erdheim Chester disease may be associated with diverse histiocytic neoplasms as Langerhans cell histiocytosis and Rosai Dorfman disease, a feature which necessitates histological confirmation and concurrence of atypical clinical manifestations [5,6].

Upon radiography, bilateral and symmetrical lesions of osteosclerosis appear confined to diaphyseal and metaphyseal cortex of long bones, preponderantly distal femur and proximal tibia.

Bone scintigraphy with 99 technetium expounds symmetrical and intense labelling of long bones of distal lower extremities and exceptionally the upper extremities [6,7].

Positron emission computerized tomography (PET CT) depicts retroperitoneal disease with thickening of perinephric soft tissue, a feature which induces the characteristic appearance of a 'hairy kidney' [6,7].

Cardiovascular disease typically depicts circumferential thickening of soft tissue vasculature, especially thoracic and abdominal aorta with the emergence of 'coated aorta'. Besides, infiltration of right atrium and atrioventricular groove may be observed [6,7].

Computerized tomography (CT) of thoracic cavity demonstrates involvement of pulmonary parenchyma with smooth thickening of interlobular septa and interlobular fissures, configuration of micro-nodules, ground glass opacities and parenchymal condensation [6,7].

Magnetic resonance imaging (MRI) of brain and cardiac tissue may be employed for initial detection of possible Erdheim Chester disease, especially asymptomatic lesions [7,8].

Agents such as vemurafenib may be employed for treating lesions demonstrating BRAF V600E genetic mutations [8,9].

MEK inhibitors as trametinib or cobimetinib may be efficaciously employed for treating lesions with diverse genetic mutations within MAPK pathway [8,9].

In the absence of administered targeted therapy, cladribine appears to be moderately efficacious [8,9].

Interferon-α, pegylated interferon-α and anticytokine directed therapy with agents as anakinra, infliximab, tocilizumab may decimate burden of disease [8,9].

Chronic Erdheim Chester disease manifests with variable prognostic outcomes, contingent to site of disease emergence [8,9].

Lesions subjected to interferon therapy demonstrate proportionate 5 years overall survival of ~68% whereas targeted therapies are associated with 5 year overall survival of ~83%. Disease confined to central nervous system (CNS) configures as a significant independent prognostic factor and independent predictor of disease associated mortality within specific survival analysis [8,9].

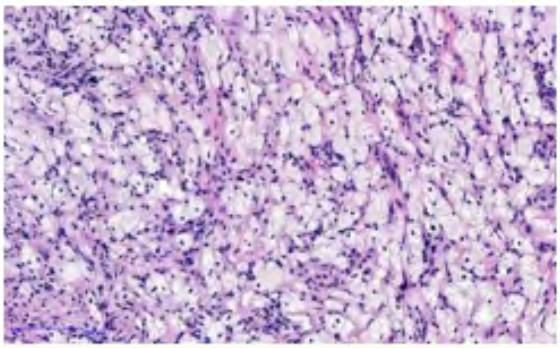

Figure 1: *Erdheim Chester disease demonstrating intense infiltration of foamy histiocytic cells intermingled with few lymphoid and plasma cells encompassed within fibrous tissue [10].*

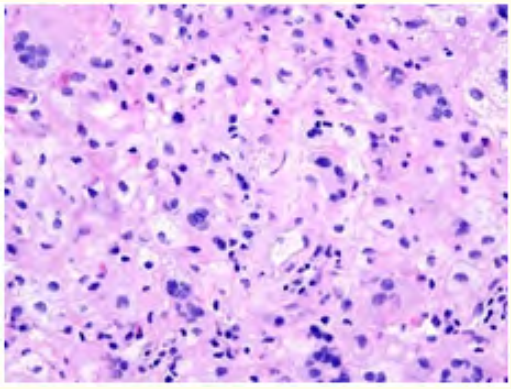

Figure 2: *Erdheim Chester disease delineating significant infiltration by foamy histiocytic cells commixed with lymphoid cells and plasma cells and surrounded by fibrous tissue [11].*

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10. Image1 Courtesy: Frontiers.com.

11. Image 2 Courtesy: Pathology outlines.

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