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Editorial

Engross and Submerge-Rosai Dorfman Disease

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Rosai Dorfman disease occurs as an exceptionally encountered, non-Langerhans cell histiocytosis accompanied by heterogeneous clinical features. An estimated 40% individuals depict extra-nodal disease which may be confined to specific sites or emerge as disseminated disease. The disorder may be familial or concur with neoplasia or immune disease.

Denominated within1960s as a self limiting condition arising within regional lymph nodes and initially scripted by Destombes as lymphadenitis with lipid excess, Rosai and Dorfman categorized the lesion as sinus histiocytosis with massive lymphadenopathy [1].

As per the contemporary and revised classification of histiocytic disorders by World Health Organization (WHO) 2016, the condition is categorized as 'R' group with nodal and extra-nodal disease and 'C' group singularly delineating cutaneous disease.

Nearly 33% lesions depict clone specific alterations within mitogen activated protein kinase or extracellular signal regulated kinase (MAPK/ERK) pathway [2,3].

Mean age of neoplastic discernment is 50 years whereas Rosai Dorfman disease may occur within 2 years to 79 years. A female preponderance is observed with female to male proportion of 1.5:1 [2,3].

An estimated up to 50% lesions may arise within regional lymph nodes whereas extra-nodal sites as cutaneous region may be implicated within 50% subjects. Besides, extra-nodal sites as bone, nasal sinuses or upper respiratory tract, orbit, retroperitoneum and sites within central nervous system as dura or brain parenchyma may be involved [2,3].

Of obscure pathogenesis and multifactorial aetiology, Rosai Dorfman disease is associated with immune dysregulation. A subset of lesions demonstrate genetic alterations within MAPK/ERK pathway, thereby indicating a pathogenesis concurrent with Langerhans cell histiocytosis and Erdheim Chester disease.

An estimated 33% of neoplasms depict repetitive, exclusive genetic mutations within KRAS and MAP2K1 genes.

Germline mutations within SLC29A3 gene may appear within familial lesions of Rosai Dorfman disease [2,3].

Clinical features are contingent to diverse disease sites and associated conditions. Classic or nodal and cutaneous Rosai-Dorfman disease frequently occur as self limited, benign disease whereas disseminated Rosai Dorfman disease may depict an aggressive biological course responsive to systemic therapy.

Clinically, the condition demonstrates a heterogeneous clinical course which is contingent to site of disease emergence [3,4].

The disorder may concur with autoimmune disorders as systemic lupus erythematosus, idiopathic juvenile arthritis, autoimmune haemolytic anaemia and neoplasia as lymphomas or myeloid neoplasms. Besides, IgG4 related Rosai Dorfman disease is typically associated with enhanced population of plasma cells immune reactive to IgG4 [3,4].

Classic Rosai Dorfman disease demonstrates enlargement of regional lymph nodes, commonly bilateral cervical lymph nodes occurring within young male subjects [3,4].

Extra-nodal Rosai Dorfman disease manifests with diverse clinical representations designated as

- Cutaneous lesions manifest as gradually progressive, painless nodules, papules or plaques.
- Neurologic symptoms as headache, seizures, motor or sensory abnormalities and disturbed gait may occur.
- Orbital symptoms as exophthalmos or visual disturbances may emerge.
- Nasal sinuses may concur with nasal congestion or nasal obstruction.
- Pulmonary symptoms appear as dry cough, dyspnoea, simulated primary lung cancer, interstitial lung disease or diverse inflammatory and infectious conditions.
- Retroperitoneal disease may represent as diffuse soft tissue infiltration and uncommonly as a discrete tumefaction along with or in the absence of hydronephrosis and ureteral obstruction.
- Multisystem disease occurs in ~20% instances wherein prognostic outcomes are contingent to quantifiable involvement of extra-nodal sites.

Rosai Dorfman disease may configure as histiocytosis concurrent with Langerhans cell histiocytosis or Erdheim-Chester disease [4,5].

Upon microscopy, a characteristic accumulation of histiocytes is observed wherein histiocytic cells are imbued with abundant eosinophilic cytoplasm and enlarged, spherical to elliptical, hypo-chromatic nuclei. Cells are frequently impregnated with engulfed, intact inflammatory cells, a phenomenon categorized as 'emperipolesis'.

Histiocytic cells confined to the lesion are encompassed with fibrosis and a significant inflammatory cell infiltrate, predominantly comprised of plasma cells and lymphocytes. Occasionally, an infiltrate of neutrophils is observed [5,6].

Typically, regional lymph nodes depict sinuses distended with lesional histiocytes. Exceptionally, Rosai-Dorfman disease may be detected as an incidental condition concurrent with lymphoma within a singular surgical specimen [5,6].

C group histiocytosis	**Malignancies**
Eruptive xanthoma	Malignant lymphoma
Juvenile xanthogranulomatoma	Malignant melanoma with distant metastasis
Solitary reticulohistiocytoma	Sarcomas and Stewart-Treves syndrome
L group histiocytosis	Anaplastic large cell lymphoma
Langerhans cell histiocytosis	Various metastatic neoplasms
Erdheim Chester disease	Autoimmune disorders
H group histiocytosis	Castleman's disease
Hemophagocytic syndrome	IgG4 disease
Infectious lesions	Gaucher's disease
Acquired immunodeficiency syndrome	Whipple disease
Granulomatosis with polyangiitis	Benign soft tissue neoplasia

Table: *Differential diagnosis of Rosai Dorfman disease [3].*

Monocytes and macrophages configuring Rosai Dorfman disease appear immune reactive to CD68, CD163 or OCT2. Besides, immune reactivity to S100 protein, cyclin D1 and BCL1 is observed.

Tumour cells appear immune non reactive to CD1a, Langerin and BRAF V600E [6,7].

Rosai Dorfman disease requires segregation from neoplasms as Langerhans cell histiocytosis, sinus histiocytosis, Erdheim Chester disease, juvenile xanthogranuloma and low grade B cell lymphoma [7,8].

Rosai Dorfman disease may be appropriately evaluated by comprehensive clinical history, physical examination, morphological features and imaging studies [7,8].

The disorder may appear in conjunction with diverse histiocytic neoplasms as Langerhans cell histiocytosis and Erdheim Chester disease. Atypical clinical manifestations necessitate disease confirmation with cogent morphological evaluation.

Positron emission computerized tomography (PET CT) of regional lymph nodes demonstrates enhanced central intake with photopenic halo [7,8].

Extra-nodal Rosai Dorfman disease expounds:

- Central nervous system manifestations as hyper-attenuation of meningeal tumefaction. Computerized tomography depicts a neoplasm with contrast enhancement.
- Skeletal lesions emerge as lytic lesions confined to medulla.
- Pulmonary involvement may represent as cystic parenchymal alterations, interstitial lung disease, tumour nodules, focal pulmonary infiltrates or airway disease.
- Nasal sinuses may manifest with thickened maxillary wall.
- Retroperitoneal lesions may represent as tumefaction confined to renal hilum and hypodense zones consistent with cellular infiltration confined to sub-capsular zone or configuration of renal cortical nodules [7,8].

Rosai Dorfman disease may be treated contingent to site of involvement and appearance or absence of cogent clinical symptoms.

Regional lymph nodes or cutaneous regions emerge as self limited disease aptly managed with simple observation.

Surgical eradication may be employed to treat symptomatic neoplasms confined to a singular site [9,10].

Multifocal and refractory lesions may necessitate systemic, first line therapy with agents as cladribine, cytarabine, methotrexate or prednisone [9,10].

Targeted therapy with MEK inhibitors may be beneficially employed in lesions demonstrating genetic alterations within MAPK/ERK pathway. Adoption of optimal, systemic chemotherapy is contingent to extent of disease [9,10].

Generally, prognostic outcomes of disease confined to regional lymph nodes and cutaneous regions are superior.

A subset of lesions with multi-focal disease may demonstrate an aggressive clinical course [9,10].

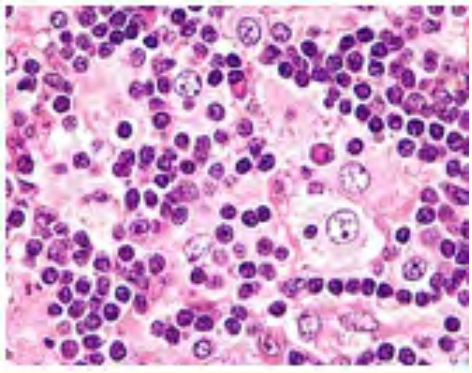

Figure 1: *Rosai Dorfman disease delineating an infiltrate of histiocytic cells imbued with abundant eosinophilic cytoplasm and spherical nuclei and are surrounded by a population of lymphoid and plasma cells. Few intact inflammatory cells are engulfed by histiocytic cells [11].*

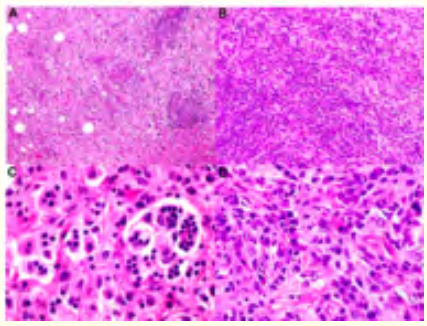

Figure 2: *Rosai Dorfman disease expounding an infiltrate of histiocytic cells impregnated with abundant, eosinophilic cytoplasm and spherical nuclei with encompassing fibrosis. Few intact inflammatory cells are engulfed by histiocytic cells [12].*

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11. Image 1 Courtesy: Libre Pathology.

12. Image 2 Courtesy: MDPI.

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