



## Review Paper

# Rosai Dorfman Disease in CNS 19 Cases from one Institute

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## **ABSTRACT**

*Rosai Dorfman Disease (RDD) is a benign idiopathic histiocytic disorder rarely occurring primarily in Central Nervous System (CNS) and is not well characterized as it mimics other lesions. Herein we report 19 cases of RDD from one institute and review the literature on RDD with CNS involvement.*

**Keywords:** *Rosai Dorfman Disease, Emperipolesis, Sinus histiocytosis with Massive lymphadenopathy.*

## **INTRODUCTION**

Originally called as lipid storage disorder (adenitis avec surcharge lipidique)<sup>1</sup> developing after inflammation. First case of sinus histiocytosis with massive lymphadenopathy (SHML) is attributed to Destombes who biopsied a 24yr old man in 1959<sup>4</sup>.

In 1969 Rosai and Dorfman coined the term SHML for clinical syndrome caused by rare benign idiopathic histiocytic proliferative disorder characterised by emperipolesis (em –inside +peri-around+ poleomai-to wander about).

The disease presents in two forms, classic and extranodal form.

Rosai-Dorfman Disease (RDD), classic form, usually manifests as massive cervical lymphadenopathy, fever raised ESR, polyclonal hypergammaglobulinemia.

Extranodal RDD involves diverse sites like skin, bone nasal cavity, orbit, upper respiratory tract, CNS, digestive system, pancreas, thyroid, breast.

The terms “Destombes-Rosai-Dorfman” or “Rosai –Dorfman” disease<sup>2</sup> are preferred to sinus histiocytosis with massive lymphadenopathy because lymphnodes are not always involved.

In CNS, sites involved are cerebral convexity, middle cranial base, parasagittal, petroclival region, suprasellar, cavernous sinuses, thoracic spine, and 90%<sup>15</sup> involve leptomeninges.

CNS involvement is rare (4 -5%)<sup>3,5,2</sup> with 75% of cases involving brain and 25% involving the spinal canal.

In CNS, disease typically manifests within the epidural or subdural compartment of the spine or skull base, with intraparenchymal involvement less common.

Paediatric CNS cases usually involve the parasphenoidal<sup>2</sup> region.

RDD in CNS is uncommon and when this occurs it mimics meningioma and presents histologically with atypical features.

The histiocytosis association of America<sup>3</sup> estimates that the disease affects one in 2,00,000 children born each year in United States.

The Central Nervous System RDD has a mean onset age of 37yrs<sup>3,4</sup>. Neurological manifestations are rare, occurring in 4%<sup>3</sup> of one series. Isolated intracranial form of RDD is very rare and may be encountered once in a Neurosurgeon's career.

## AETIOLOGY

The aetiology of RDD<sup>8</sup> is unknown although a viral pathogenesis is postulated. Numerous reports have identified Human herpes virus 6(HHV-6) in visceral and cutaneous lesions. However HHV-6 has frequently been found in many reactive and infectious disorders of lymphoid tissue, and its presence in RDD is nonspecific.

Immunophenotypic profiling and studies of monokine expression suggest an origin from activated macrophages, which have been shown to produce IL-1beta and TNF- alpha.

Infection<sup>5</sup> has been suggested as an underlying cause, but a definitive agent has never been isolated. Molecular studies using polymorphic regions of the human and rogen receptor locus have demonstrated that RDD is a polyclonal disorder<sup>5,8</sup>.

Epstein-Barr virus and Human herpes virus-6 were detected by in situ hybridization<sup>9</sup> in some cases.

Molecular studies in two women with RDD have revealed polyclonal X-inactivation patterns, thus implying that this disorder is reactive rather than neoplastic.<sup>2</sup>

To date 90<sup>3</sup> cases of RDD are described in CNS in literature which were misdiagnosed as granuloma or neoplastic (meningioma like lesions.).

Most patients with RDD usually have an indolent course<sup>2</sup>. Extra nodal RDD tends to be chronic and relapsing<sup>12</sup>.

In the past treatment of RDD has been primarily surgical and despite surgical treatment relapse of CNS RDD has been reported in 14%<sup>4</sup> of cases.

In cases with relapse adjuvant treatment with radiotherapy and or chemotherapy has been instituted with success.

Combinations of adjuvant chemotherapy includes cyclophosphamide, vinblastine, etoposide and methotrexate.

Surgical resection is the most effective treatment with complete resolution of the disease after total removal of the lesion.

Prognosis of CNS RDD is good .

Our study is aimed mainly to diagnose RDD histopathologically and immunohistochemically and differentiate it from other mimics.

Our study is done because of the rarity of the disease in CNS

## MATERIALS AND METHODS

There are totally 19 cases with age ranging from 15-65 years which included 10 males and 9 females .All cases had relevant clinical history and radiological findings.

Haematoxylin and Eosin stained slides are studied in all cases, crush smears and frozen sections were done in 9 cases. Special stains, Zeihl Neelson for acid fast bacilli, PAS and GMS for fungal organisms were done in all cases.

Immunoperoxidase evaluation using the avidin-biotin-complex method was performed using a panel of antibodies S100, CD-1a,CD-68 on all cases.

### IHC-METHODOLOGY

Representative sections measuring 3-5 microns was taken from formaldehyde fixed paraffin embedded tissue.

Slides were placed on a cleaned and sialinised glass slide.

Slides were labeled with diamond pencil and kept in the incubator at 37C overnight.

Slides were put into xylene (3 changes each 5 minutes) and then absolute alcohol (2 changes each for 3 minutes) for deparaffinisation.

Endogenous peroxidase activity is blocked using 3%H<sub>2</sub>O<sub>2</sub> in methanol for 30 min. slides are washed in running tap water for 15 min.

Then slides are rinsed in distilled Water for 10 minutes.

Heat mediated antigen retrieval is done by Antigen retriever EZ. The slides are placed in the plastic container containing about 275ml of sodium citrate buffer (0.01M, pH 6) at boiling temperature 95C, for 10 min. each in 2cycles.

Slides are washed in running tap water for 20 min.

Then slides are rinsed in distilled water for 5min.

Then washed with two rinses of TBS pH 7.6 for 5min. each Sections are covered with normal human serum for monoclonal (1/10) dilution, swine serum for polyclonal (1/10) dilution- called protein block.

The blocking serum solution is tipped off the slide and replaced with 100-200 micro litre of primary antibody for 45 min.

The slides are then washed with 3 changes of TBS solution for 5min. each.

Sections are covered with second layer antibody biotinylated mouse immunoglobulin 1/400 Rabbit immunoglobulin 1/600 dilution at room temperature

The slides are then washed with 3 changes of Tris buffer solution for 5min each.

Sections are then covered with streptavidin 1/800 dilution for 45 min at room temperature. Slides are then rinsed with 3 changes of Tris buffer solution for 5min each.

Sections are covered with DAB solution for 5-15 min at room temperature.

The slides are then rinsed with distilled water for 5min then running tap water for 5min.

The sections are counterstained with Harris Haematoxylin for 30sec to 1 min, and then washed with running tap water.

Place the slides in Scott's solution for 3min.

Slides are washed with distilled Water and then dehydrated by taking through 90% alcohol, absolute alcohol 2 changes and xylene 2 changes 1min each.

### Mount with DPX solution.

TABLE – I			
ANTIBODY USED	SOURCE	TYPE	DILUTION
S -100	DAKO	R	1:400
CD -1a	NOVACAST	M	PRE DILUTED
CD -68	DAKO	M	PRE DILUTED
R -Rabbit, polyclonal M-Mouse, monoclonal			

## REVIEW OF LITERATURE

Extranodal RDD involvement occurs in approximately 43% of cases<sup>4,5</sup> either alone or in association with lymphadenopathy.

Most common sites are paranasal sinuses, orbit, CNS (spine, skull base) skin, upper respiratory tract.

In CNS intracranial involvement is twice as common as spinal involvement.

RDD confined to CNS occurs between 20 to 40 yrs of age, mean age -37yrs<sup>3</sup> with a slight male predominance.

Franco paredes and Kelly Martin<sup>6</sup> presented a case of RDD in CNS (57 yr old lady) which on magnetic resonance imaging showed abnormal areas of leptomeningeal enhancement and possibilities included infectious meningitis, leptomeningeal carcinomatosis and meningioma.

Meningeal biopsy was undertaken, suspecting a neoplastic process, frozen sections showed nodular aggregates of lymphoid cells initially interpreted as malignant lymphoma. Permanent sections and IHC revealed RDD.

The study concluded that RDD could mimic chronic meningitis or meningioma and RDD should be in the differential diagnosis of patients with dural based masses and diffuse leptomeningeal enhancement on MRI.

Tavangar, Ali Mahta and colleagues<sup>7</sup> reported CNS RDD in 79 yr old man, which on imaging was given as compatible with meningioma or leptomeningeal carcinomatosis.

Frozen section was interpreted as inflammatory pseudotumor or lymphoma.

The above study concluded that RDD may mimic the clinical presentation of meningitis, meningeal carcinomatosis or meningioma, but it has a benign course with very good response to steroids.

Katerine, Min Wang,<sup>8</sup> reported 45yr old patient with enhancing mass in parietal lobe as a plaque like lesion adherent to a layer of brain parenchyma, which on imaging was reported as meningioma.

They concluded that primary RDD of CNS is rare, occurs in 4th-5th decade, 2/3 of cases may have systemic involvement and uncommonly RDD manifests as isolated parenchymal involvement without dural involvement, intraparenchymal lesions are almost always solitary and much less common.

Kinoshi, Ibayashi et al<sup>9</sup> reported a case of RDD presenting as lesion involving surface of frontal lobe, falx cerebri and basal region with sulci underlying lesion being obscured (greater involvement in subarachnoid space than in the overlying dura). With the extensive involvement clinical Differential diagnosis en plaque and malignant meningioma, metastatic carcinoma, sarcoidosis were made and histopathologically lymphoma, LCH, plasma cell granuloma were thought. On frozen section plasma cell granuloma was given. The study concluded that RDD may show an unusual imaging pattern and histopathology, IHC is essential to permit a firm diagnosis.

Yachnis<sup>10</sup> presented case of 35 yr old man with bilateral contrast enhancing masses, consistent with meningiomas which on histopathology turned out as RDD and was confirmed by IHC.

Wood rock and colleagues<sup>11</sup> reported RDD of suprasellar region in 15yr old girl, presenting as enlargement of pituitary infundibulum with extension into adjacent areas (suprasellar cistern, optic chiasma). Differential diagnosis included suprasellar germinoma, LCH and metastasis. The study concluded that RDD usually manifests in epidural or subdural compartment and intracranial involvement is twice as common as spinal region. It also concluded that with CNS involvement there is a reported increase in immunologic abnormalities -47 % with involvement of CNS versus 22% in those without such involvement, portending a poor prognosis.

Yu-Ting Huang, et al<sup>12</sup> reported a case of RDD with metachronous nasal and intracranial presentation. The study included 49yr old pt who first presented with sinonasal RDD, underwent surgical excision.

Follow up 1yr later showed recurrence of para nasal mass with intracranial dura based mass exhibiting hypointense foci on T2 weighted imaging.

The study concluded that strongly enhanced dura based intracranial mass with hypo intense foci on imaging may provide diagnostic clues towards RDD preoperatively and surgery is the most commonly accepted mode of treatment.

Federico Di Rocco and colleagues<sup>2</sup> reported a case of RDD involving cerebral hemisphere in 13 yr old child, which had rapid clinical and radiological progression. An inflammatory process was suspected and subtotal excision by burr hole was done.

Lesion recurred 3 months later, presented as huge mass which was excised enbloc and examination revealed emperipoleosis. Pediatric cases of CNS RDD are rare and usually indolent.

The study quotes list of pediatric cases where parasphenoidal region was mostly involved. The study concluded that diagnosis of RDD remains a challenge as noted by lack of specific diagnosis following first procedure in this case.

RDD occurred in children in age group of 5 -15yrs<sup>2</sup> with commonest locations being cavernous sinus, sphenoid, frontal, para sphenoid region.

Concurrent lymph node involvement was not seen in all the cases and surgery was the usual mode of treatment followed by steroids and radiation therapy.

Zahir, Rahmat and Shojaiee<sup>13</sup> reported a case of rare presentation of RDD in 42 yr old woman, who presented with left sided loss of vision.

The lesion was diagnosed as meningioma and operated. 4yrs later patient presented With right visual loss and cough. Multiple adenopathies were seen on CT chest.

A Differential diagnosis of sarcoidosis or meningiomatosis was made on MRI. Biopsy suggested granulomatous disease such as tuberculosis.

The study concluded that etiology of RDD remains obscure, affects higher age group has male preponderance and differential diagnosis of tuberculosis, fungal infection can be considered when RDD presents with polymorphous infiltrate with abscess formation.

Petzold et al<sup>4</sup> reported 2 cases of relapsing intracranial RDD, which were radiologically diagnosed as multiple meningiomas and operated. Complete removal was not possible by surgery and the lesion recurred, which were subjected to radiotherapy.

The study concluded that post operative low dose radiotherapy is advisable in cases with subtotal tumor resection or recurrence of neurological symptoms. The study also concluded that in literature review, recurrence of RDD was reported as around 14% as of date and a follow up period of 5yrs including brain imaging is advisable, which is the median relapse time in intracranial RDD.

Christopher, Justin Brown, et al<sup>14</sup> reported a case of intracranial RDD regressing following corticosteroid therapy. A 53yr old male presented with multiple intracranial dura based lesions including lesion at planum sphenoidale and tuberculum sella compressing optic nerves, from Cerebello pontine angle to foramen magnum compressing brainstem and lesion at C-2.

MR imaging was consistent with multiple meningiomas and orbitopterional craniotomy and optic nerve decompression with maximum debulking was done. Frozen section and final pathological analysis showed lesion composed of histiocytic cells positive for S-100 and CD-68.

Post operatively the patient was kept on regimen of decadron, followed by prednisolone in tapering dose and there was complete resolution of the disease.

The study concluded that corticosteroid agents should be considered as a viable treatment option in patients with intracranial RDD, lending support to hypothesis that RDD is an immunological disease process.

Andriko et al<sup>5</sup> study is credited for having described 11 cases of RDD isolated to Central Nervous System. Lesions were most often extra axial and dura based and diagnosed most often on imaging as meningiomas. The study concluded that RDD of central nervous system had predilection for males presenting in 4-5 decade, unlike nodal which occurred in mostly 20.6yrs.

The lesion in CNS presents difficulties, as emperipolesis is less apparent and fibrosis, a common feature of extranodal sites, obscures histiocytic proliferation.

The study also concludes that RDD has been misdiagnosed or under diagnosed in the past and recommends that before rendering diagnosis of plasma cell granuloma RDD-CNS should be excluded through careful evaluation for emperipolesis and S100 immunostaining.

Finally, it says that Rosai dorfman disease is to be included in the differential diagnosis of fibrotic chronic inflammatory lesion of CNS and surgical resection appears to be most efficacious approach.

Purav, K Ganapathy and colleagues<sup>15</sup> reported study of 10 cases of RDD of CNS in age group of 18 -60 years with a slight male predominance. The lesions mostly presented as dura based masses involving parietal, parieto-occipital, frontal areas, consistent with meningiomas on imaging.

The study concluded that RDD in CNS is uncommon, cannot be distinguished from meningioma either radio logically or preoperatively and diagnosis is thus entirely based on histopathology and IHC. The study also concluded that prognosis of RDD with CNS involvement is not poor and most of the lesions are completely curable by surgery.

Yin Wang and colleagues<sup>16</sup> reported 6 cases of RDD in CNS, misdiagnosed as meningioma on imaging and histopathology showed characteristic emperipolesis by histiocytes which are S-100 positive.

Wu, M Anderson, Kahn<sup>17</sup> in their study revealed, RDD of CNS misdiagnosed as nonspecific inflammatory process because of atypical histological features. They concluded, saying familiarity with atypical features and appropriate use of IHC stains is required for definitive diagnosis of RDD.

Kimm and prias, et al<sup>18</sup> reported a case of multiple meningeal nodules presenting with seizures mimicking multiple meningioma clinicoradiologically, histopathological findings of which confirmed diagnosis of RDD.

Natarajan et al<sup>19</sup> reported a case of RDD which occurred as primary intracerebral lesion and reported clinically, as glial neoplasm, radiologically as lymphoma.

Kumar KK menon, nair<sup>20</sup> reported a case of RDD which was mistaken for chronic subdural haematoma.

Kinoshita, Yasukouchi and others<sup>21</sup> reported RDD in CNS mimicking pachymeningitis. (Thickened stratified dura with associated cortical oedema.)

Ture, Sekar and colleagues<sup>22</sup> showed on histology RDD, which was misdiagnosed as pseudotumor.

Crush smear cytology reported by KT Chen<sup>23</sup> prepared intra-operatively from small portion of biopsy specimen showed histiocytes characteristic of RDD showing lymphophagocytosis.

The study reported that crush cytology appears useful alone or in conjunction with frozen section in intraoperative diagnosis of RDD.

Jhonston Jm and brown<sup>24</sup> reported a case of RDD in CNS diagnosed as, Lhermitte Duclos disease radiologically.

## **OBSERVATION AND RESULTS**

In our prospective and retrospective study of 15 yrs duration (1996 – 2011) at Apollo Specialty Hospital, Chennai, 19 cases of RDD in CNS were diagnosed, without evidence of other sites of involvement.

The cases included 10 males and 9 females (Table-2), age group ranged from 15 to 65yrs (Table-3).

The lesions are mostly extra-axial and dura based (17 cases), 1 case was extra dural, involving C3- C4 level of spine, 1 case presented with multiple intracranial lesions (Table-4).

Patients with intracranial lesions presented clinically predominantly with headache, seizures, visual disturbances, tingling and numbness (Trigeminal). Patient with spinal disease presented with spastic quadriparesis and Left hand paraesthesia (Table-5).

Clinical and radiological diagnosis was meningioma in 15 cases ,in 2 cases differential diagnosis eosinophilic granuloma/meningioma was given ,in another 2 cases tuberculoma/ meningioma was diagnosed.

Radiologically RDD presents as isointense lesion on T1 weighted images, which enhances on administration of contrast( Gadolinium )

RDD lesions mimic meningiomas radiologically showing hypointensity on T2 weighted images. Meningiomas show low to high signal intensity on T2 weighted MR images.

In our study of 19 cases relative components of inflammation, fibrosis and emperipolesis are analysed.

Histologically the lesions are grouped based on the relative proportions of various components (Table-8).

Inflammation is being grouped into 3 types:

- Cases with predominantly thick fibrocollagenous tissue separating the inflammatory cell infiltrate in the form of nodules are termed –Nodular (Fig 1 & 2)
- Cases with less amount of fibrosis but with predominantly diffuse infiltration of inflammatory cells are termed –Diffuse ( Fig 3 & 4)
- Cases with both the above pattern of inflammation are termed –Mixed. (Fig 5)

Number of histiocytes with emperipolesis were studied under high power field. (Fig 6)

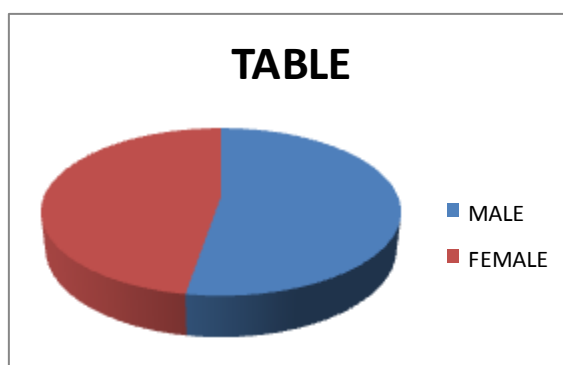
When rare histiocytes exhibited emperipolesis it is grouped 1+, when occasional cells were seen 2+ and more than occasional cells 3+.

Fibrosis is grouped into 1+, 2+ or 3+ depending on whether it is mild, moderate or marked.

We observed that there is no statistically significant features in all these groups .However nodular and mixed type showed relatively less histiocytic cells with emperipolesis and IHC stains were particularly helpful in better appreciation of the same.

**TABLE – 2**

GENDER	INCIDENCE
MALES	10
FEMALES	9
TOTAL	19

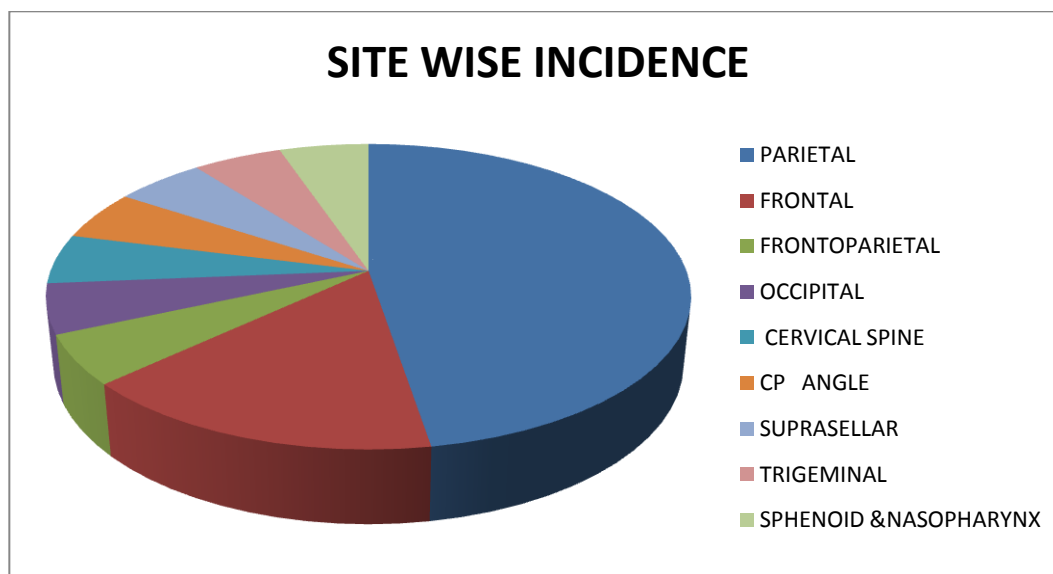


**TABLE – 3**

AGE WISE INCIDENCE	
1-10	0
11-20	3
21-30	0
31-40	6
41-50	6
51-60	3
61-70	1

**TABLE – 4**

SITE WISE INCIDENCE	
PARIETAL	9
FRONTAL	3
FRONTOPARIETAL	1
OCCIPITAL	1
CERVICAL SPINE	1
CP ANGLE	1
SUPRASELLAR	1
TRIGEMINAL	1
SPHENOID &NASOPHARYNX	1



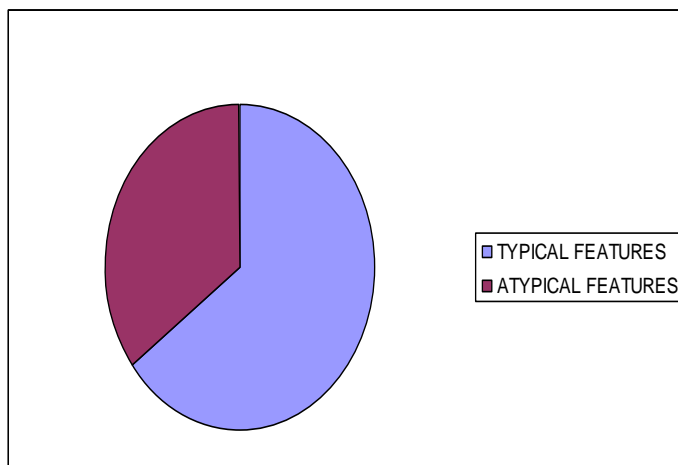
**TABLE - 5**

Clinical Features	No of Cases
Headache	10
Generalised Seizures	12
Spastic Quadripareisis	1
Vertigo,Giddiness,Blurred vision	1
Spastic hemiparesis,Dysphasia	2
Tingling&Numbness,pain on Lt.side of face	1



**TABLE -6 HISTOLOGY**

Typical features	13
Atypical Features	6



**TABLE - 7**

IMMUNOHISTOCHEMISTRY			
CASE NO.	S-100	CD -68	CD 1a
1	+	+	-
2	+	+	-
3	+	+	-
4	+	+	-
5	+	+	-
6	+	+	-
7	+	+	-
8	+	+	-
9	+	+	-
10	+	+	-
11	+	+	-
12	+	+	-
13	+	+	-
14	+	+	-
15	+	+	-
16	+	+	-
17	+	+	-
18	+	+	-
19	+	+	-

TABLE - 8			
S NO.	INFLAMMATION	FIBROSIS	EMPERIPOLEISIS
CASE 1	Diffuse	+	++
CASE 2	Diffuse	++	+
CASE 3	Mixed	+	+++
CASE4	Nodular	++	+
CASE 5	Diffuse	+	++
CASE6	Mixed	++	++
CASE7	Mixed	++	+++
CASE8	Diffuse	+	++
CASE9	Mixed	++	+++
CASE10	Mixed	++	+
CASE11	Nodular	+++	+
CASE12	Mixed	+	++
CASE13	Nodular	+++	++
CASE14	Diffuse	+	+++
CASE15	Mixed	++	+++
CASE16	Nodular	+++	+
CASE17	Diffuse	+	+
CASE18	Diffuse	+	+
CASE19	Nodular	+++	+



Fig 1 – Scanner view showing predominantly thick fibrocollagenous tissue separating the inflammatory cell in the form of nodules ( H & E - 4X )



Fig 2 – Low Power view of Nodular infiltrate ( H & E - 10X )

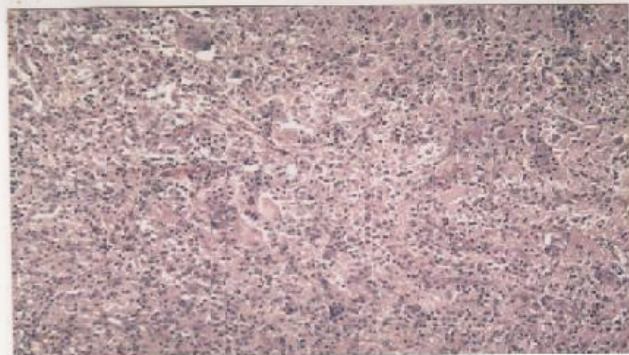


Fig 3 – Low Power view showing less amount of fibrosis predominantly diffuse infiltrate of inflammatory cells ( Diffuse ) ( H & E - 4X )

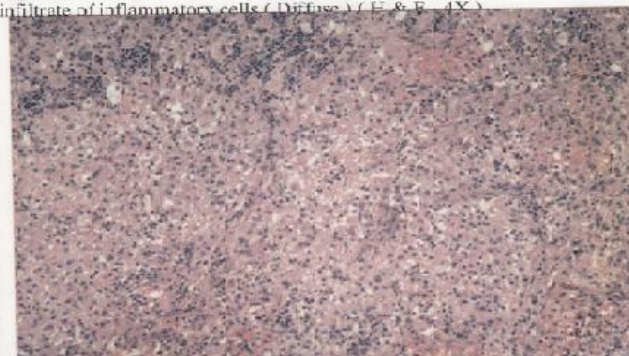


Fig 4 – Another Low Power view of diffuse infiltrate ( H & E - 10X )



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Fig 5 – Scanner view showing mixed pattern of inflammation

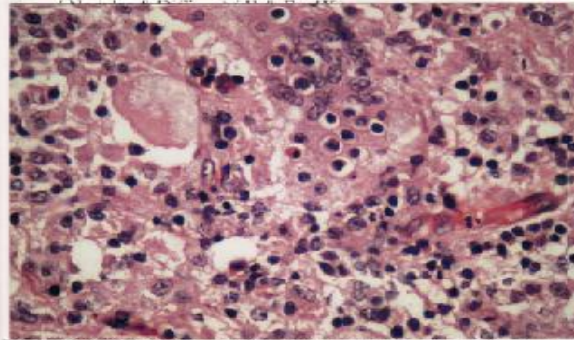
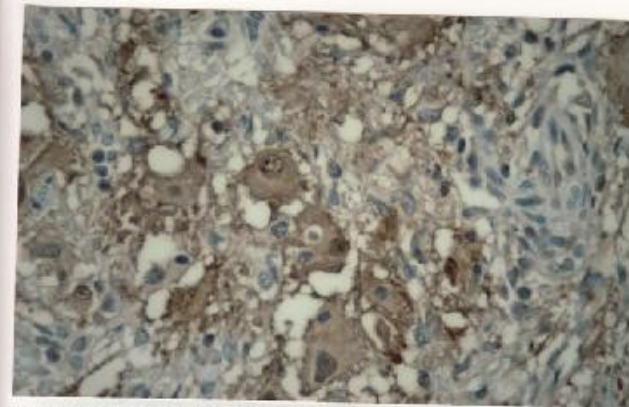


Fig 6 – High Power view showing Lymphocytes, plasma cells & Histocytes with evidence of emperipolesis (Lymphoplaguecytosis) ( H & E - 40X )



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Fig 7 – Immunohistochemistry for S100 protein showing immunoreactivity ( 40X )

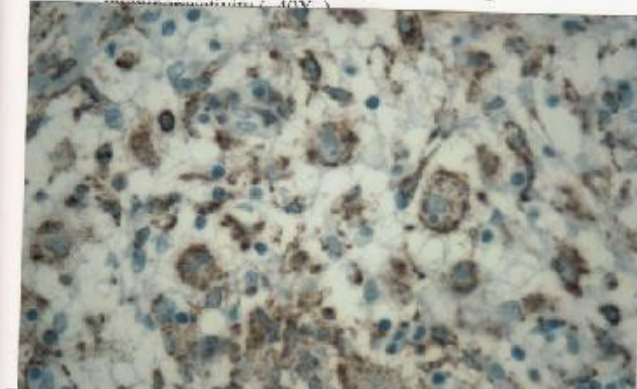


Fig 8 – Immunohistochemistry for CD 68 showing immunoreactivity ( 40X )

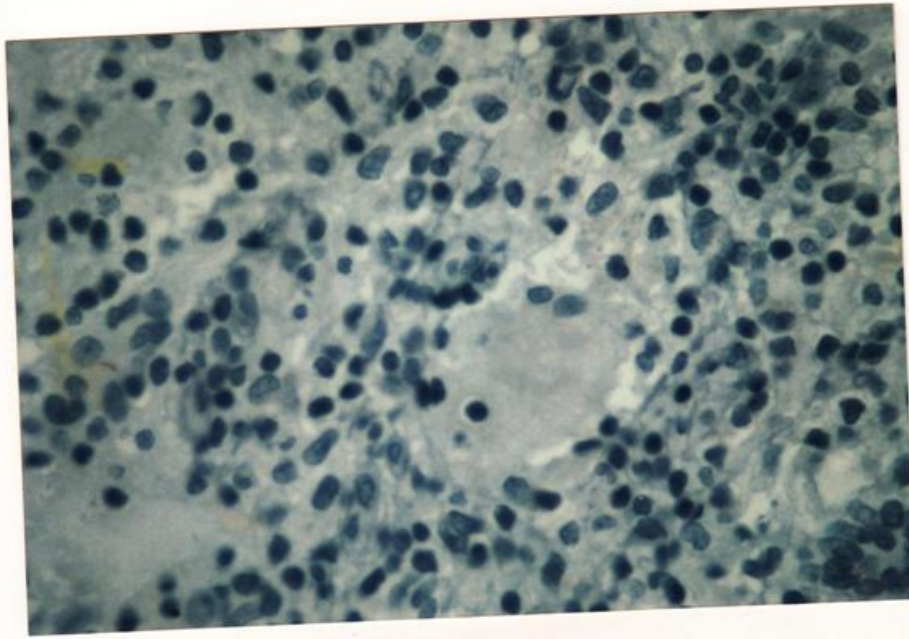


Fig 9 – Immunohistochemistry for CD 1A showing no reactivity ( 40X )

## DISCUSSION

RDD or (sinus histiocytosis with massive lymphadenopathy) SHML is triad of massive cervical lymphadenopathy, expanded lymph node sinuses and characteristic histiocytes showing emperipolesis.

Extranodal involvement occurs in more than 43%<sup>5</sup> of patients. Most common sites are paranasal sinuses, orbit, spine, skull base, skin, and upper respiratory tract.

2/3 of CNS cases are not accompanied by lymphadenopathy.

RDD in CNS is mostly diagnosed as meningioma radiologically. The role of pathologist is to keep RDD in the differential diagnosis of dura based lesion and to confirm by immunohistochemistry.

IHC is an auxiliary diagnostic procedure in histopathology for identification, visualisation of previously undetected cell components in tissue sections, cell smears and cytospins by application of immunological principles and techniques to the study of cells and tissues.

The goal of this study is to document the clinico pathologic features of 19 cases of RDD-CNS and to describe criteria for distinguishing this disorder from similar appearing infectious, neoplastic and nonspecific reactive conditions.

Pathogenesis: It is an idiopathic non neoplastic disease of either an autoimmune aetiology or a reaction to a yet unidentified infectious agent.

Imaging reveals dural-based extra-axial contrast enhancing masses that often elicit vasogenic edema in the underlying brain.

Review of reported intracranial RDD revealed that 2/3 had no lymphadenopathy, and 50% had no associated systemic disease.

The symptoms at presentation reflect the site of disease and include seizures, headaches, cranial nerve deficits, and paraparesis. Rare cases with sellar involvement have presented with symptoms related to pituitary dysfunction.

The histologic features of RDD-CNS are similar to those of lymphnodes. Cytologically the infiltrates are composed of variable numbers of histiocytes intermixed with plasma cells and lymphocytes. Emperipolesis, consistent finding in nodal disease is often less apparent in CNS (extranodal site). Fibrosis is another feature common in extranodal site.

The histiocytes have moderate to abundant pale eosinophilic cytoplasm, with vesicular nuclei with nucleoli and may show emperipolesis. The large pale histiocytes of RDD are immunoreactive for S-100, CD-68, alpha-1 antitrypsin, but negative for CD1a.

Histologic differential diagnosis includes meningioma, especially lymphoplasmacytic type, Langerhans cell histiocytosis, lymphoproliferative disorders, Plasma cell granuloma, Wegeners granulomatosis and infectious diseases.

Lymphoplasmacytic meningioma elicits pronounced chronic inflammatory reaction which may be confused with infiltrates of RDD-CNS, but recognition of typical meningioma histology along with EMA immunostaining differentiates two processes. Meningiomas are variably positive for S-100 and positive cells should not be interpreted as RDD associated histiocytes.

Lymphoproliferative disorders show characteristic erythrophagocytosis rather than lymphophagocytosis. Further more aggressive lymphoproliferative disorders will show frank atypical cytology of the mononuclear cells.

LCH is characterized by lobated nuclei and longitudinal nuclear grooves and prominent infiltrate of eosinophils. Eosinophils are rarely observed in the cellular infiltrates of RDD. On immunohistochemistry, histiocytes of LCH are CD-1a positive and Birbeck granules are seen on electron microscopy.

RDD-CNS with fibrosis may have distinctly nodular appearance suggestive of Nodular sclerosing variant of Hodgkin's disease. Reed Sternberg cells and its variants, lack of emperipolesis and negative S-100 and positive CD-15 and CD-30 help to clinch the diagnosis.

Plasmacytoma in CNS can be distinguished by demonstrating that plasma cell infiltrates are monoclonal and hence neoplastic.

Lack of sheet like necrobiotic type necrosis and necrotizing capillaritis should exclude Wegeners.

Absence of small well formed granulomas makes sarcoidosis less likely.

Plasma cell granuloma lacks characteristic emperipolesis and S-100 immunostaining.

This study confirms that RDD cannot be distinguished from meningioma preoperatively and thus diagnosis of RDD is entirely based on histopathology, immunohistochemistry.

The largest study in literature is by Andriko et al<sup>5</sup> in which 11 cases of RDD in CNS were diagnosed with slight male predominance, age range of about 22-63yrs. The lesions were most often extra-axial and dura based with clinical and radiological diagnosis of mostly meningioma. None of the patients were febrile or demonstrated any lymphnode involvement.

The study by Yin Wang and colleagues<sup>16</sup> consisted of 6 patients presenting with RDD in CNS, which are diagnosed as meningiomas clinically and radiologically.

The study by Purav and colleagues<sup>15</sup> included 10 cases of RDD in CNS with 8 males and 2 females, age range of 18 to 60 yrs, which are diagnosed as meningioma clinically and radiologically.

In our study 19 cases with 10 males and 9 females was observed (Table-2). This may be an observation bias, due to being a tertiary care centre.

Similar to earlier studies our study comprised of age group ranging from 15 to 65 yrs (Table-3) and most of the lesions are clinically diagnosed as meningioma. In case of the trigeminal lesion, schwannoma was considered. One patient had multiple intracranial lesions suggestive of metastases. None of the patients had fever or lymphadenopathy. One patient had raised ESR (Table-9).

The radiological diagnosis was meningioma in 15 cases, in 2 cases eosinophilic granuloma or meningioma was given. In another 2, Tuberculoma or meningioma was considered.

Frozen section diagnosis was reported in 7 cases, given as chronic inflammatory lesion, with dense lymphoplasmacytic infiltrate. In one case chronic necrotizing granulomatous inflammation was reported.

In earlier studies by Andriko et al<sup>5</sup>, Yin wang and coworkers<sup>16</sup>, Purav and colleagues<sup>15</sup> histological diagnosis of RDD in CNS was made when variable number of histiocytes with abundant cytoplasm and emperipolesis were seen, over shadowed by lymphoplasmacytic infiltrate and fibrosis.

The above studies concluded that RDD in CNS presents difficulties as emperipolesis is less apparent and fibrosis obscures histiocytic proliferation.

In our study similar histologic features were seen.

Most of the lesions showed typical histologic features of fibrocollagenous tissue with infiltrate of mature lymphocytes, plasma cells, occasionally neutrophils and eosinophils, along with variable number of histiocytes.

The histiocytes showed indistinct cell borders, abundant pale eosinophilic cytoplasm which was fine to coarsely vacuolated. The nuclei were round to oval, vesicular with nucleoli. Some of the histiocytes were multinucleated. Unequivocal emperipolesis could be identified in 11 cases. (Fig 6)

6 cases showed atypical histologic features showing marked fibrosis obscuring the usual morphology of RDD. In these cases emperipolesis was very difficult to appreciate in Haematoxylin and Eosin. (Table-6).

In such cases with atypical histologic features, immunohistochemistry using S-100 and CD-68 protein immunostaining increased the visibility of histiocytes (Table-7) (Fig 7 & 8).

These histiocytes are negative for CD-1a (Fig 9) which constitutes a reliable marker for LCH thus eliminating LCH which is the most histological mimic of RDD.

An attempt was made to group the cases into diffuse, nodular and mixed based on relative amount of chronic inflammatory cells, histiocytes with emperipolesis and relative fibrosis (Table-8). No significant correlation could be seen, except that in cases with more fibrosis, prominent emperipolesis is difficult to appreciate and IHC in particular is helpful in increasing the visibility of histiocytes.

Treatment modality was surgery in all cases. The patient with cranial and spinal lesions underwent near total excision of the lesions. The small intracranial lesion was left unexcised.

Follow up ranging from 3 months to eight years was available in 11 cases. The patient with multiple lesions died in 10 days after biopsy due to underlying cardiac disease. Seven patients had no evidence of disease progression and remained asymptomatic.

One patient with a left medial frontal convexity lesion developed axillary lymphadenopathy two years after surgery, however, histopathology revealed tuberculosis of lymph node.

**TABLE – 9**

S NO	AUTHORS & YEARS	NO OF CASES	AGE GROUP	SEX	LOCATION	LYMPHNODE INVOLVEMENT
1	Andriko, et al; 2001	10	22 - 63 Yrs	7M,4F	8 - Intracranial	No
2	Yin Wang, et al; 2009	6	NA	NA	5 - Intracranial & 1 Spinal	No
3	Purav P, et al; 2005	10	18 - 60 Yrs	8M,2F	9 - Intracranial 1 - Spinal & Intra - cranial	No
4	Petzold, et al 2001	2	78, 47 Yrs	M,M	Intracranial	No
5	Our Study	19	18 - 65 Yrs	9F,10M	18 - Intracranial (1 - Supra sellar) & 1 - Spinal	No

M- Male ; F- Female; NA – Not Available

**CONCLUSION**

Rosai-Dorfman disease (RDD) is a rare primary CNS lesion .In CNS the rate of incidence is <1% of tumors. Incidence of RDD occurring primarily in CNS is only 4-5% of the total RDD occurring in the body. 19 cases (M : F ::10:9) are seen in the last 15 years (1996 – 2011) in our institution. Almost all cases are clinically and radiologically diagnosed as Meningioma with rare diagnosis of eosinophilic granuloma and tuberculoma. RDD should be considered as differential diagnosis for all dura based contrast enhancing CNS lesions. Histopathology shows a fibro inflammatory lesion with emperipolesis in variable proportions. Immunohistochemistry is mandatory for confirming the diagnosis.

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S NO.	AGE/SEX	H P NO.	HISTOLOGICAL FEATURES
1	60/F	H96 - 538	Fibrocollagenous tissue containing dense infiltrate composed of mature lymphocytes,numerous plasma cells & histiocytes. Many histiocytes have vesicular nuclei with pale cytoplasm,emperipolesis.Few lymphoid follicles seen .
2	37/M	H98 -1190	Predominantly diffuse & focal nodular infiltrate of lymphocytes, plasma cells, histiocytes.Occassional histiocytes show emperipolesis.
3	37/M	H98 -1447	Several foci of pale macrophages,lymphocytes, plasma cells. Some larger ganglion -like cells with eosinophilic cytoplasm and phagocytosed nuclear debris and lymphocytes. Fibrous bands.
4	50/M	H00 -651	Foci of pale macrophages, and plasma cells.Occassional histiocytes show emperipolesis.
5	56/F	H00 -3201	Thick flattened collagenised fibrous tissue with lymphocytes, plasma cells and large histiocytes. Few of the histiocytes show emperipolesis.
6	15/F	H01 -106	Fibroadipose tissue and bony spicules with polymorphous infiltrate of lymphocytes, plasma cells, many hemosiderophages, few histiocytic cells with large vesicular nuclei, prominent nucleoli &pale eosinophilic cytoplasm. Rare emperipolesis is seen.
7	39/M	H03 -464	Sheets of histiocytes,plasma cells and lymphocytes,with emperipolesis within histiocytes.
8	18/M	H03 -3178	Fibrovascular tissue with dense aggregates and diffuse infiltrate of lymphocytes and mature plasma cells.
9	31/M	H04 -1038	Brain tissue with overlying dural tissue showing dense diffuse infiltrate of mature lymphocytes,plasma cells. Focal areas show aggregates of neuron like histiocytes some of which show emperipolesis.stroma is fibrotic.
S NO.	AGE/SEX	H P NO.	HISTOLOGICAL FEATURES
10	40/F	H04 -3319	Fibroadipose tissue with polymorphous infiltrate of lymphocytes, plasmacells,few multinucleate giant cells,& few histiocytic cells large vesicular nuclei,prominent nucleoli,pale eosinophilic cytoplasm. Rare emperipolesis seen.
11	17/F	IH06 -626	Dural tissue infiltrated by inflammatory cell infiltrate of lymphocytes,plasma cells, & histiocytes, few of them show emperipolesis.
12	35/M	H06 -2467	Predominantly nodular infiltrate of lymphocytes, plasma cells, histiocytes.Occassional histiocytes show emperipolesis.
13	60/F	H07 -8459	Diffuse infiltrate of lymphocytes,plasma cells and large histiocytes.The histiocytes show abundant cytoplasm with vesicular nuclei and prominent nucleoli with emperipolesis.
14	65/F	H07 -6603	Nodular infiltrate of lymphocytes,plasma cells, and histiocytes.Occassional large histiocytes show emperipolesis.
15	44/F	H08 -3776	Thick fibrocollagenous tissue with lymphocytes, plasma cells,and few large cells with abundant cytoplasm, with vesicular nuclei with prominent nucleoli.Many of the histiocytes show emperipolesis.
16	44/F	H08 -7066	Fibrocollagenous tissue infiltrated by mixed inflammatory cell infiltrate of lymphocytes,plasma cells, scattered multinucleate histiocytes .Occassional histiocytes show emperipolesis.
17	45/M	H09 -1336	Fibroadipose tissue with polymorphous cell infiltrate of lymphocytes, plasma cells ,histiocytes. Occassional histiocytes show emperipolesis.
18	54/M	H10-3216	Fibrocollagenous tissue containing dense infiltrate composed of mature lymphocytes,numerous plasma cells & histiocytes. Many histiocytes have vesicular nuclei with pale cytoplasm,emperipolesis.
19	42/M	H11-658	Several foci of pale macrophages,lymphocytes, plasma cells. Some larger ganglion -like cells with eosinophilic cytoplasm and phagocytosed nuclear debris and lymphocytes.