Neurological Presentations and CNS Pathology of Rosai-Dorfman disease: A 28-Year Report and Review from Single Tertiary Referral Institute in Thailand

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Abstract

Rosai-Dorfman Disease (RDD) is a benign systemic histio-proliferative disorder with a variable clinical presentation, depending on the sites of the lesion. Intracranial RDD is a form of sporadic extranodal type of RDD and usually occurs without lymphadenopathy. Most intracranial lesions are attached to the dura mimic meningioma; therefore, pathology is necessary to diagnose this rare entity. Pathology of RDD is characterized by numerous large histiocytic cells engulf the intact lymphocytes (Emperipolesis). Immunohistochemical stains of histiocytic cells are positive for CD68, S-100 protein but negative for CD1a. Surgery is the first line of treatment and post-operative corticosteroids or chemotherapy may be recommended in some cases. This article describes and summarizes the four cases of intracranial RDD encountered by the Neurological Institute of Thailand from 1992 to 2019 and highlights the clinical presentations, pathology, plan of treatments and outcome of disease in each occurrence.

Keywords: craniotomy, dural-based tumor, intracranial tumor, Rosai-Dorfman disease, sinus histiocytosis

Abbreviations

CBC - Complete blood count
CNS = Central nervous system
CPA - Cerebello-pontine angle
EMA - Epithelial membrane antigen
GFAP - Glial fibrillary acidic protein
MRI - Magnetic resonance imaging
RDD - Rosai-Dorfman disease

Rosai and Dorfman initially described RDD as a separate entity in 1969 as characterized clinically by massive bilateral cervical lymphadenopathy, fever, leukocytosis, raised erythrocyte sedimentation rate (ESR). Histological examination of the lymph node revealed sinuses containing large histiocytes with intact phagocytosed lymphocytes (emperipolesis).[1] Epidemiological reports of RDD are extremely rare. Regarding its intracranial location, this disorder can mimic meningioma radiologically. We review our experience in the management of our four cases of intracranial RDD, both in their clinical presentation and histopathological findings. We also present a review of current modern histiocytic classification, etiological hypothesis and a brief description of treatment.

Case Report

Case # 1

A 44-year-old man with 14 years' history of asymptomatic rheumatic heart disease (mitral stenosis) presented with right sensorineural hearing loss and neck pain radiating to the right side. He had no history of headache or fever. Denied ataxia or tinnitus. No palpable lymph nodes detected. Other neurological exam was not remarkable. The preoperative magnetic resonance imaging (MRI) showed multiple nodules at the right cerebello-pontine angle (CPA) and fifth – seventh cervical vertebral area. The right CPA mass was 1.7x1.8x1.3 cm in

size. No dilatation of the internal acoustic canal (Figure1A). The patient was operated in two episodes; the first surgery was laminectomy of C5-7 with subtotal resection. The second surgery (right retrosigmoid craniotomy) was done five months after first surgery. Both of the tissues revealed similar microscopic findings (Figure1B).

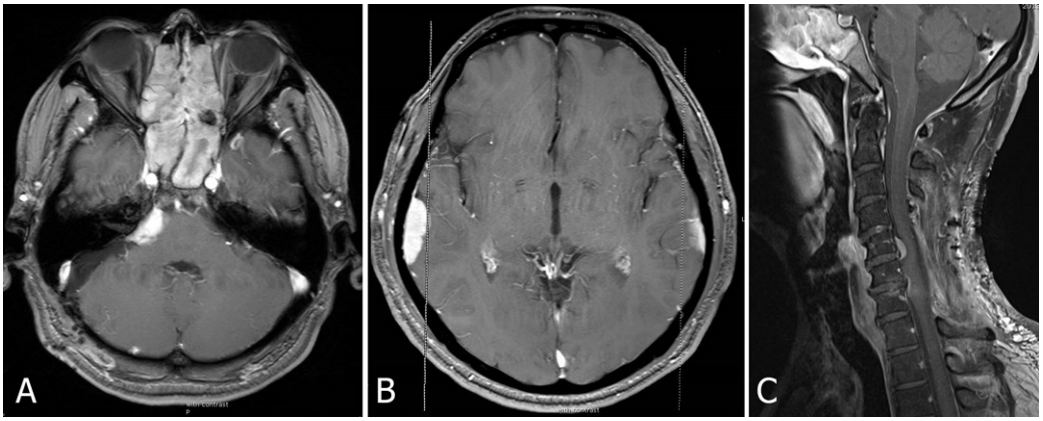

Figure 1A: Preoperative T1 weighted gadolinium (Gd) enhanced MRI of case # 1. Axial MRI showing multiple nodules at right CPA (A), bilateral temporal area (B). Sagittal MRI (C) demonstrating multiple dural-based enhancing nodules at C5-7 with cord compression.

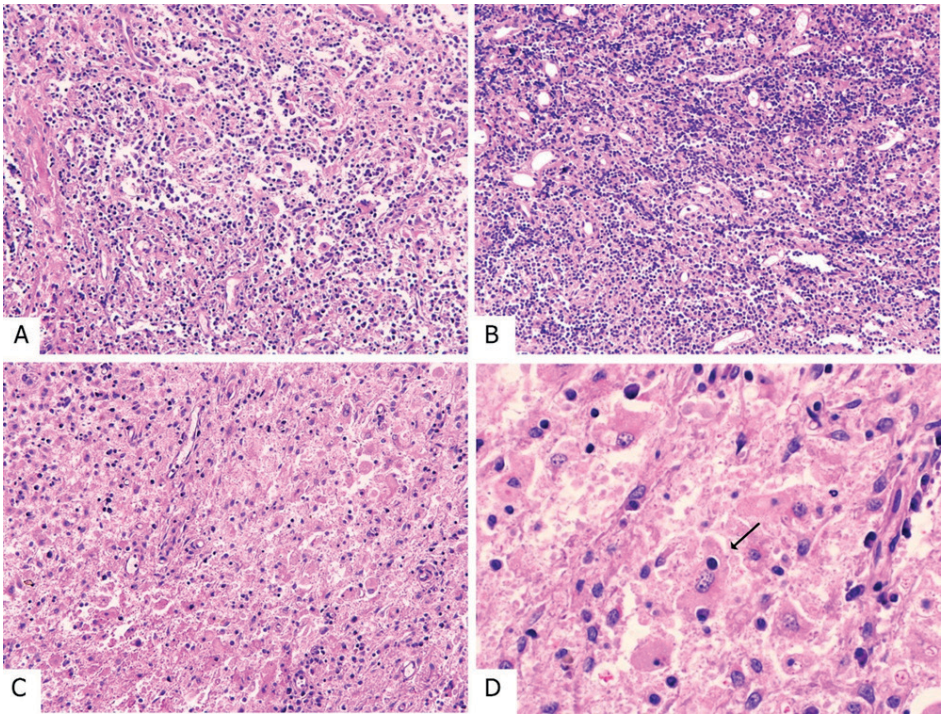

Figure 1B: Photomicrographs of case#1
A: Diffuse lymphohistiocytic proliferation (Hematoxylin &Eosin, 400X)
B: Densely lymphocytic infiltration with sinus-like dilatation (Hematoxylin & Eosin, 400X).
C, D: Photomicrographs show numerous large histiocytic cells with emperipolesis(arrow) (C; Hematoxylin & Eosin, 200X, D; 600)

After the second surgery, the patient had a runny nose and high fever. Repeated MRI revealed haziness of the right mastoid air-cells, right mastoid antrum and right middle ear cavity. Intravenous antibiotic was administered for pansinusitis (Figure 1C-A). Eight days later, the rhinorrhea stopped. He was discharged 20 days after surgery. A follow-up MRI showed progression of intracranial lesions (Figure 1C-B-D). The patient was transferred to a hematologist at another hospital for adjuvant chemotherapy (Vinblastin and Prednisolone). At the eight-month follow up examination, the patient was symptom free.

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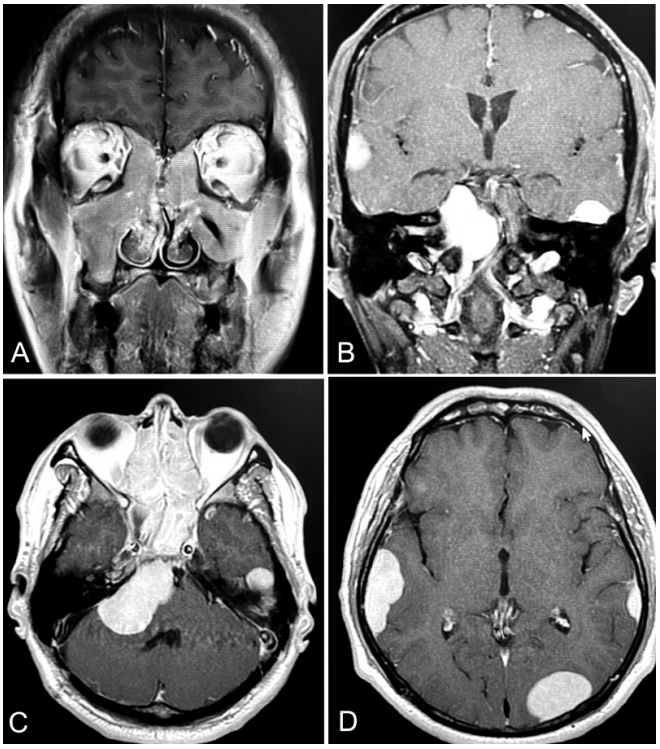

Figure 1C: (A) Coronal T1-weighted image showing haziness of mastoid air-cells. (B-D) Postoperative T1-weighted image with Gd-enhanced showing progression of right CPA mass, measured 28.8x3.0x3.5 cm. Other non-resected residual lesions were unchanged as compared to prior study. (B: coronal view, C&D: axial view, respectively).

Case # 2

A 51-year-old man with eight years' history of hypertension, presented with headache and progressive loss of vision over two years. Visual acuity was 20/20 and 0/20 in the right and left eye, respectively. Both pupils were 4 mm and not reacting to light. Fundi were pale. Neurological examination showed loss of sensation on the distribution of left V1-V3. There was no sign of facial palsy. His hypertensive disease had been controlled by Atenolol and HCTZ for 10 years. MRI scan showed a large dural-based mass at the left sphenoid wing, which measured 5 cm in maximal diameter, encased left second and third cranial nerves (Figure 2A). Based on the radiological findings, the provisional diagnosis was meningioma. The patient underwent left pterional craniotomy with subtotal resection. Pathological study was done (Figure 2B). After operation, he had problem of secondary adrenal insufficiency. Daily hydrocortisone was injected and he was discharged 13 days later. At 6-month follow-up, MRI examination showed residual lesion (4x3.9x4.7 cm), with extension to left optic nerve and resulted in chronic left optic neuropathy. A follow-up MRI nine months later showed no significant change in size of the lesion. Patient lost to follow-up.

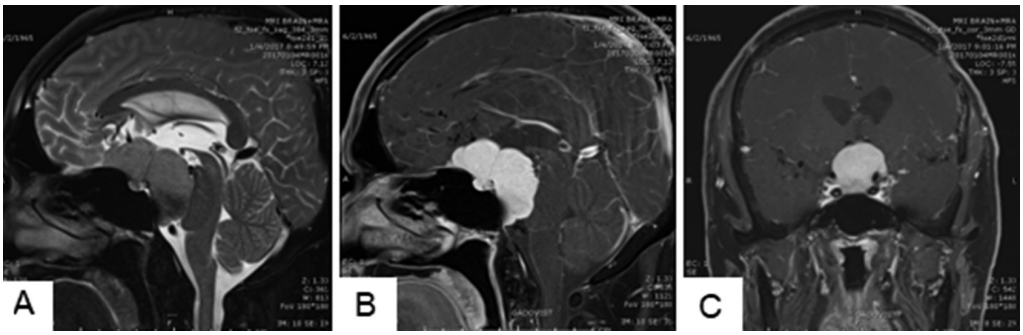

Figure 2A: Sagittal fat suppression T2-weighted image (A) and sagittal (B), coronal (C) Gd-enhanced fat suppression T1-weighted image demonstrated a meningeal-based mass at planum sphenoidale, suprasellar region and retroclivus which appeared isointensity on T2Wi with homogeneous enhancement.

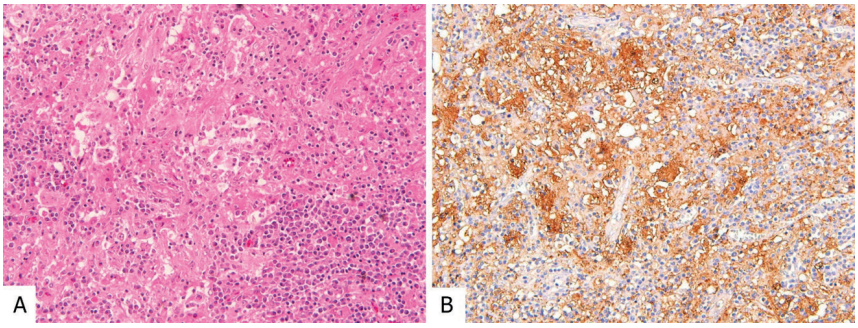

Figure 2B: Photomicrographs of case#2 showing accumulation of large histiocytes in collagenous background (**A**: Hematoxylin &Eosin, 200X; **B**: S100, 200X).

Case # 3

A 58-year-old woman with no history of fever or epilepsy in the patient's family presented with episodes of focal seizure on the right side of body over a period of one month. The patient received primary care at another hospital and was administered Phenytoin (Anti-epileptic drug). An emergency computed tomography (CT) scan found a mass at left parietal convexity with dural based, suspected of meningioma. MRI revealed a lobulated dark mass, size 3.8 x 5.5 x 0.8 cm (Figure 3A). A left frontal-parietal craniotomy with subtotal resection was done. Although the patient was doing well three days post-surgery, she complained of slurred speech but had no evidence of seizure and was discharged 11 days after her surgery. At 6-month follow-up, her speech had improved. An MRI examination at 24 months post-operation showed a residual lesion at resected calvarial lesion with no interval change in size. (Figure 3C)

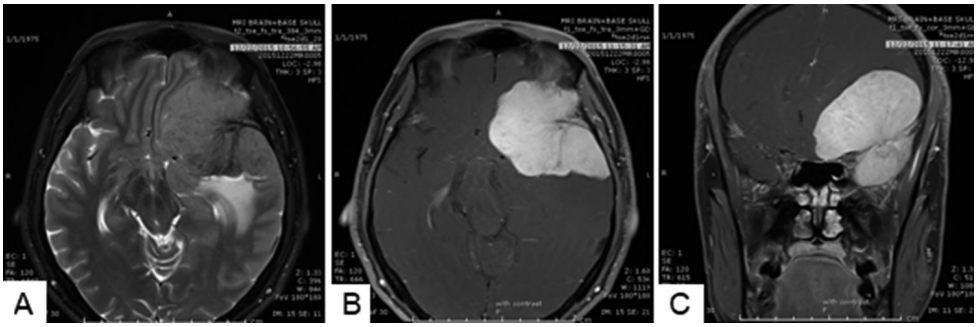

Figure 3A: Axial fat suppression T2-weighted image (A) and axial (B), coronal (C) Gd-enhanced fat suppression T1-weighted image demonstrated a meningeal-based mass at left anterior and middle cranial fossa which appeared isointensity on T2WI with homogeneous enhancement.

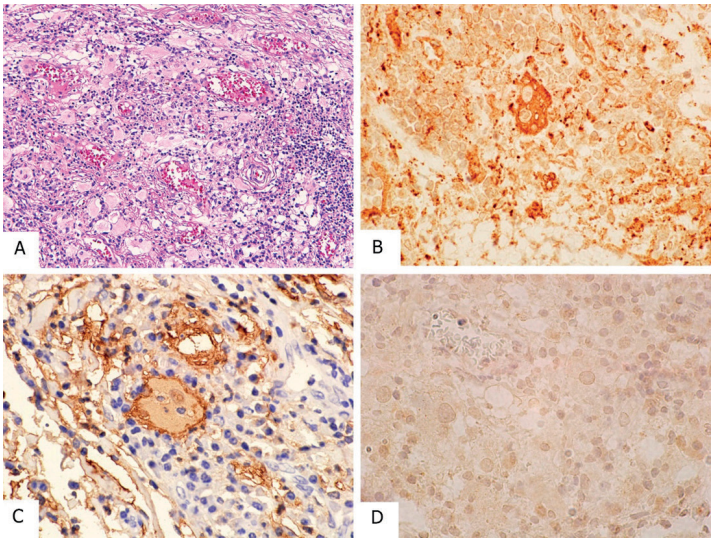

Figure 3B: Photomicrographs of case#3 showing numerous large histiocytic with emperipolesis. (A: Hematoxylin &Eosin, 200X B: CD68, 600X, C: S100, 600X, D: CD1a, 600X).

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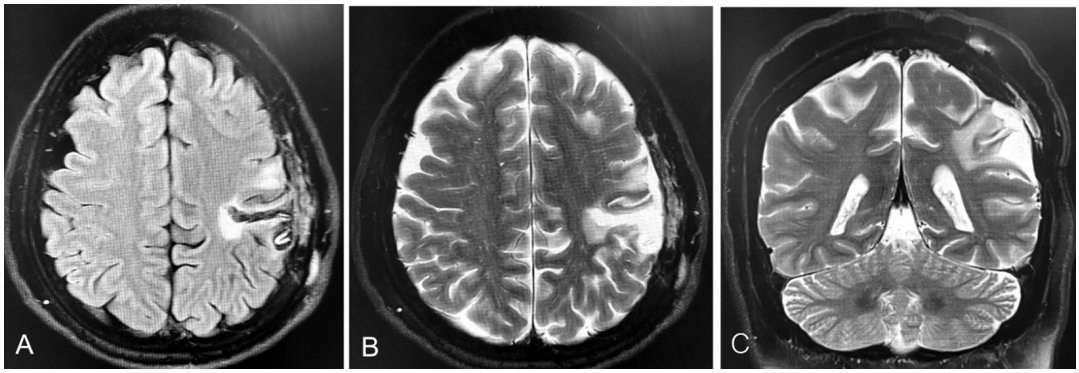

Figure 3C: Axial T2-weighted image (A, B), coronal (C) demonstrated a small nodular dural lesion at posterior left parietal lobe. Encephalomalacia at left fronto-parietal lobe associated with evidence of old hemorrhage is noted.

Case # 4

A 40-year-old man complained of blurred vision for one month. Visual acuity was 20/20 and 20/20, both right and left eyes. Pupils were 3 mm and reacted to light with no deficit in eye movement. Neurological examination showed loss of sensation on the distribution of left V1-V3. No motor weakness or lymphadenopathy. His immune status was normal. Complete blood count (CBC) showed mild leukocytosis (total white blood cells 17,400/mL, neutrophil 85.6%, lymphocytes 10.1%). An MRI showed a mixed iso-hypointense T2 extra-axial mass at the right sphenoid wing, which measured 6 x 6.5 x 5.3 cm, with homogeneous contrast enhancement. The mass extended medio-inferiorly and impinged on left pre-chiasmatic optic nerve (Figure 4A). The preliminary diagnosis was meningioma, and the mass was partially resected by pterional approach.

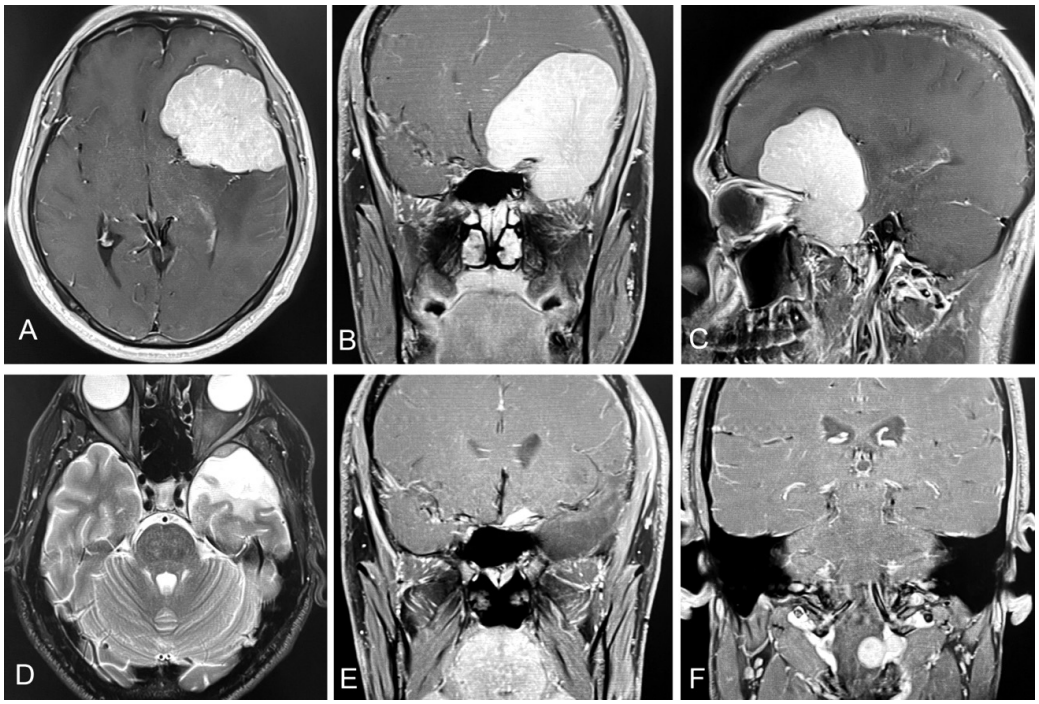

Figure 4A: Preoperative axial T1-weighted image (A), coronal (B), sagittal (C) demonstrated a large extra-axial mass with uncal herniation, attached at left orbital roof, left anterior clinoid process and sphenoid wing. noted Postoperative axial T2-weighted image showed residual lesion(D). Postoperative T1-weighted images showed focal residual lesion(E), incidental intra-extradural nodule at left side of C2 level, extended to L2 neural foramen with cord displacement (F).

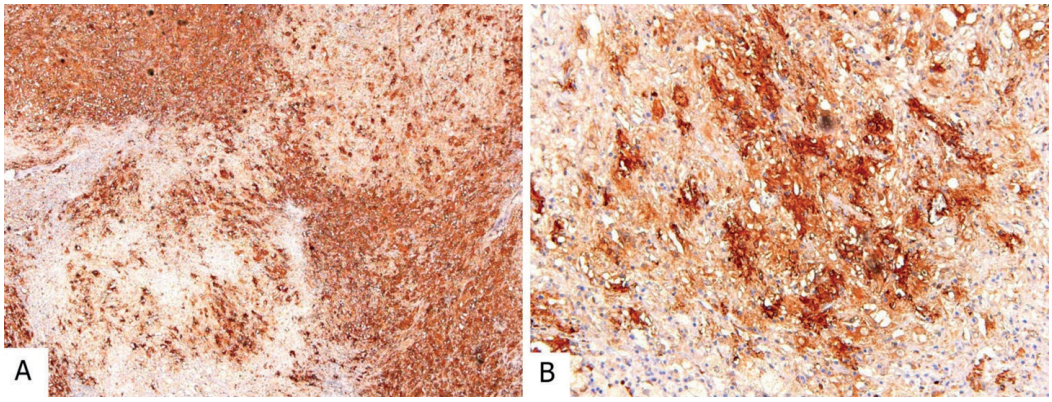

Figure 4B: Photomicrographs of case#4 showing S100-positive histiocytic aggregation, giving a nodular appearance. (A: 40X, B: 200X, respectively)

The patient was doing well post-operatively and was discharged 13 days after surgery. A follow-up MRI examination six-months later showed focal residual lesions along the left anterior clinoid process, left sphenoid wing, and medial aspect of the left orbit. New incidental lesion is found at left side of C2 level, measured 0.8x0.8x0.9 cm. Patient was sent to other hospital for treatment consultation but no drug regimen given. Unfortunately, patient lost to follow-up.

Discussion

Rosai and Dorfman[1] described this lesion of the lymph node as "**Sinus histiocytosis with massive lymphadenopathy**." But as these findings might occur anywhere in the body, this term was deleted in the published 2021 CNS World Health Organization (WHO) classification. Here we represented CNS involvement of RDD, and all four cases presented as enhancing dural-based mass, which had been diagnosed preliminary as meningioma. Many authors found that distinguishing RDD from meningioma clinically is quite difficult.[2,3] Moreover, there is a report of multiple lesions of RDD which is very rare.[4,5] In our series, there is one case (case #1), that presented with multiple nodules in both intracranial and intraspinal locations. The clinical summary of all four cases is presented in Table 1.

Table 1: Summary of clinical data of RDD cases

case	Sex	Age(y)	Chief complaint	Location	Treatment	Outcome
1	M	44	• Right SNHL • 1 year	• Right CPA • C5-7	• ST excision • CMT	• Complication: Pansinusitis • 24 months, no progression
2	M	51	• Diplopia • 2 years	• Left sphenoid wing	• ST excision • Steroids	• 9 months, no progression
3	F	58	• Focal seizure • 1 month	• Left parietal convexity	• ST excision	• 86 months, no progression
4	M	40	• Diplopia • 1 month	• Right sphenoid wing	• ST excision	• 6 months, no progression

Abbreviation: M =Male, F= Female, y years, SNHL =Sensorineural hearing loss, CPA= Cerebellopontine angle, C =Cervical spine, ST= Subtotal, CMT =Chemotherapy

The clinical presentations of intracranial RDD depended on the locations of the mass. Case #1 complained of sensorineural hearing loss, caused by the eighth cranial nerve of compression at the CPA. Case #2 and #4 presented with visual problems, caused by compression of visual nerve pathway (second and third cranial nerves in case #2 and pre-chiasmatic area of second cranial nerve in case #4). Case #3 presented with seizure due to cerebral cortex irritation. Apart from intracranial lesion, Case #1 also had small intradural-extramedullary lesions of RDD, which produced local neck pain, but absence of motor weakness or sensory deficit caused by spinal cord compression.

According to previous reports, the CNS involvement of RDD is rarely associated with lymphadenopathy[6]. All four of our cases did not show any lymphadenopathy through repeated physical exams were carried out as well.

The histological findings are similar in all four cases, which demonstrated mixed inflammatory infiltrates of small lymphocytes and plasma cells. There are large foamy histiocytes, which have large vesicular nuclei and abundant pale cytoplasm. A hallmark of RDD is "Emperipolesis", which is demonstrated by histiocytes engulfing lymphocytes or plasma cells. There is no evidence of necrosis or mitotic activity in all four cases.

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Table 2: Summary of immunohistochemical findings of four RDDs

case	CD68	S100	CD1a	GFAP	EMA
1	+	+	-	-	-
2	+	+	-	N/D	N/D
3	+	+	-	-	-
4	+	+	-	-	-

+ positive, - negative, N/D =not done

Through immunohistochemistry, the histiocytes were positive for CD68 and S100 protein, but negative for CD1a. Additionally, CD45, Glial fibrillary acidic protein (GFAP) and Epithelial membrane antigen (EMA) were added, in order to exclude other intracranial diseases such as lymphoma, glioma and meningioma, respectively. S100 protein helps in highlighting the Emperipolesis, which outlines the intracytoplasmic lymphocytes within the histiocytic cells, while negativity for CD1a helps in differentiating RDD form Langerhans cell histiocytosis (LCD).

Data by Emile et al,[7] divided the histocytoses into five groups, designated L (Langerhans), C (cutaneous and mucocutaneous), M (malignant), R (Rosai-Dorfman), and H (hemophagocytic). RDD belong to R groups (Table 3) and intracranial RDD is categorized as extranodal RDD. Common sites of extranodal RDD are skin, nasal cavity, bone, and CNS (especially dura).[7,8] Ocular involvements (case#4 of our case) is rarely found in literature (8.5%).[9,10] For no apparent reason, intracranial RDD is usually attached at the dura and mimic meningioma[11]. Moreover, IgG4-related disorder must be excluded in cases presenting with numerous IgG4-positive plasma cells.[12] Emile et al[7] recommend evaluating IgG4-positive plasma cells in all RDD cases. Unfortunately, none of our cases underwent IgG4 study as this is not yet available in our institution.

Although the etiology of RDD is poorly understood, there have been publications supporting the clonality of disease. Diamond et al[13] reported that both nodal and extranodal RDD (except cutaneous type) has kinase mutation, and *KRAS* and *MAP2K1* mutations are found in up to 33% of cases.[14] Interestingly, BRAF mutation has been found with high incidence (about 50%) in other histiocytosis (Langerhans cell histiocytosis and Erdheim-Chester disease), but only 3 have been found out of 94 RDD cases. Those 3 cases are nodal and systemic RDD. No BRAF mutation has been reported in CNS RDD[6]. Recent data by Jin et al, reported that two lesions of dural RDD has common mutations and it is believed that RDD is a clonal histiocytic disorder driven by genetic alterations[15].

The treatment of choice for RDD is surgery. The outcome of sporadic RDD (including CNS involvement) is good, with recurrence reported in only up to 50% of the cases.[16] However, 5% to 11% of patients may die of their disease.[7] Regarding CNS RDD, surgical excision may be required in unifocal cranial/spinal lesion.[17] Close follow-ups with laboratory tests is recommended every three to six months for the first two years after diagnosis. After two years, patients should visit the hospital at yearly intervals.[18] Patients with multifocal irresectable

Table 3: Entities comprising R groups (Adapted from the revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages by Emile et al.,[7] representing the Histiocyte Society)

R Group
Familial RDD
Sporadic RDD (non-cutaneous)
• Classical (nodal) RDD
• Extranodal RDD (bone, CNS, single organ, disseminate)
• Neoplasia-associated RDD
• Immune disease–associated RDD
• Other non-C, non-L, non-M, and non-H histiocytoses

CNS - central nervous system

lesions may need systemic therapy such as steroids, sirolimus, radiotherapy, chemotherapy. However, there currently is no standard regimen.[17,19] Steroids have a role in patients with CNS RDD, but need monitoring closely for recurrence once steroids are discontinued.[20,21] Intracranial RDD cases in our institution have had good outcomes, with only one case of recurrence after subtotal excision. Targeted therapy with tyrosine kinase inhibitor (Imatinib) and anti-CD20 monoclonal antibody (Rituximab) have been used in systemic RDD. MEK-inhibitors (Cobimetinib) may be beneficial in refractory or aggressive cases.[22-24] However, more studies are needed to provide information and support for FDA approval.[25-26]

Conclusion

Intracranial RDD is a rare histiocytic disorder and its clinical presentation mimics meningioma and other inflammatory condition (pachymeningitis). CNS RDD usually presents as isolated/multiple dural mass without other extracranial/nodal presentations. Neurosurgeons need to include this disorder in the differentials of dural-based lesions. Moreover, serum IgG4 should be investigated in all RDD cases, in order to exclude IgG4-related disorder. Due to the variability of clinical manifestations, pathological examination remains the standard of diagnosis. Surgical resection is necessary to treat compressive parenchymal symptoms and to establish a definite diagnosis.

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Ethics in publishing

Informed consent of this study was obtained by institutional review board of Neurological Institute of Thailand (IRB #64004).

Declaration of interest

No financial relationship to disclose.

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