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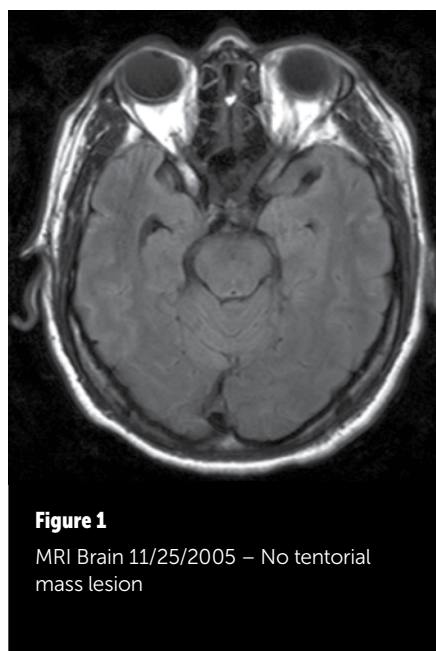


Figure 1

MRI Brain 11/25/2005 – No tentorial mass lesion

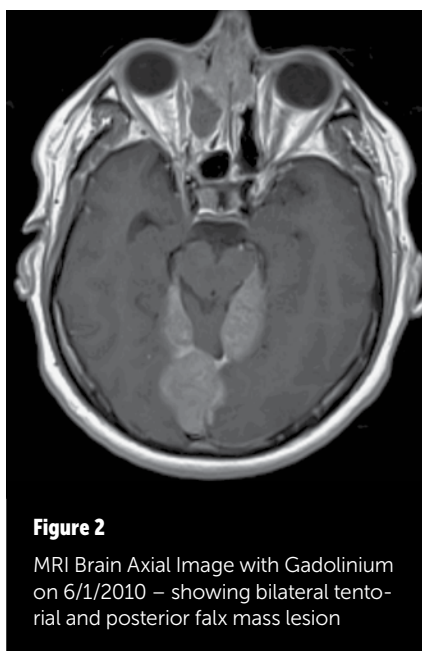


Figure 2

MRI Brain Axial Image with Gadolinium on 6/1/2010 – showing bilateral tentorial and posterior falx mass lesion

INTRODUCTION

The histiocytoses are a group of clinically diverse diseases distinguished from one another based on the specific immunophenotype of the lesional cells, implying derivation from the same precursor cell. Langerhans cell histiocytoses (LCH) diseases stem from abnormal dendritic cell lineages, while the non-Langerhans cell histiocytoses (non-LCH) are usually derived from an abnormal monocyte/macrophage cell line.¹ Non-LCH with central nervous system (CNS) involvement is predictive of poor outcome. Histopathology is used to make a diagnosis of non-LCH. Immunohistochemistry and the clinical setting are used to differentiate between the various subtypes of non-LCH.¹ The non-LCH can be divided into cutaneous non-LCH, cutaneous with a major systemic component, and systemic non-LCH.¹ Erdheim-Chester disease (ECD) and Rosai-Dorfman disease (RDD) are systemic non-LCH diseases.

First described in 1930, ECD is characterized by xanthogranulomatous accumulations. The extent of infiltration is heterogeneous and can include skin, bones, lungs, kidneys, and the CNS. Approximately 500 cases have been reported so far.² The majority of ECD patients harbor an activating mutation of the proto-oncogene BRAF, namely

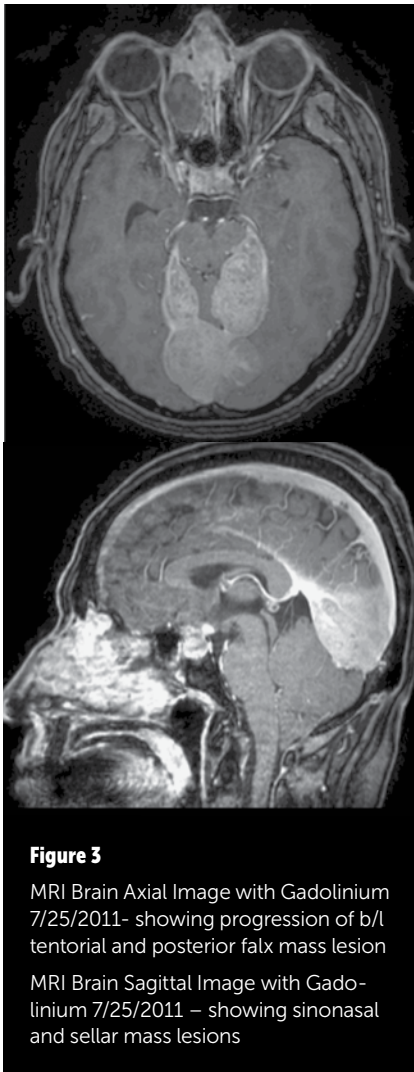
BRAF-V600E.³ Recent studies indicate CNS involvement as a predictor of highest mortality among ECD patients.⁴

First described in 1969, RDD is characterized by accumulation of histiocytes exhibiting emperipolesis in lymph nodes, in the head and neck or in extranodal sites. Extranodal sites include the CNS, skin, soft tissue and gastrointestinal tract. The clinical presentation is typically painless cervical lymphadenopathy with leukocytosis and a fever.⁵ The etiology of RDD is unknown.⁶ RDD with CNS involvement is rare and approximately 210 cases have been reported. CNS involvement typically lacks extracranial lymphadenopathy and resembles meningioma radiologically and clinically.¹ Select cases have demonstrated a combined presentation of ECD and RDD.²

In this report we describe a rare case presenting with headache and with clinically and pathologically overlapping features of RDD and ECD. We describe treatment and complications and review the existing literature regarding diagnosis and treatment for these rare conditions.

CASE REPORT

The patient is a 46-year-old gentleman from Mexico who was initially admitted to the Neurology service at Jefferson Hospital for Neuroscience in November 2005 with headache, vertigo, nausea and vomiting and was found to have bilateral vertebral artery dissection with proximal basilar artery thrombosis (MRI Picture, Figure 1). He was started on anticoagulation and discharged home. In June 2010 he presented to the neurosurgery office with worsening headaches and a MRI of the brain showed bilateral tentorial and posterior falcine mass suggestive of meningioma (MRI Picture, Figure 2). The mass was surrounding the incisura.

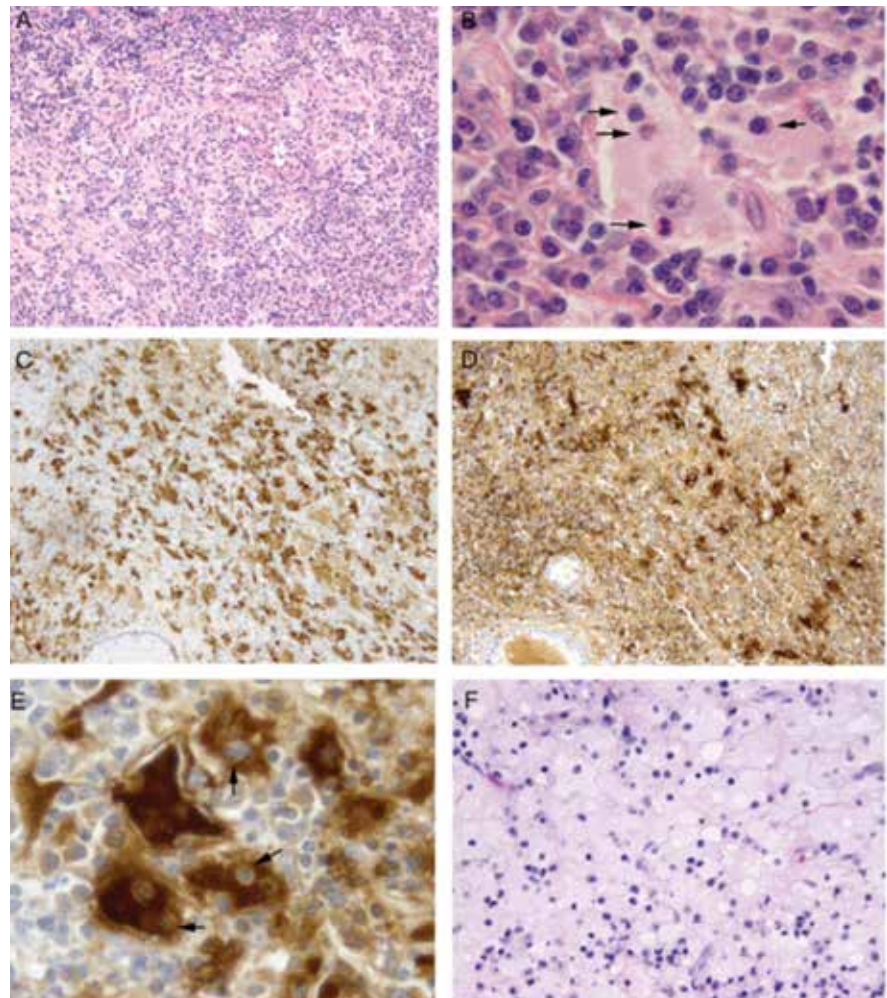
**Figure 3**

MRI Brain Axial Image with Gadolinium 7/25/2011- showing progression of b/l tentorial and posterior falx mass lesion

MRI Brain Sagittal Image with Gadolinium 7/25/2011 – showing sinonasal and sellar mass lesions

He also had an enhancing lesion in the ethmoid sinus. He was recommended to have a procedure for tissue diagnosis but he failed to do so and was lost to follow up.

In July 2011 he represented to the Jefferson Hospital ER with worsening symptoms and new onset diabetes insipidus. MRI brain, MR angiogram and CT sinus showed progression of the tentorial mass and a new sellar mass in the region of the pituitary gland and extensive sinonasal soft tissue mass extending into the right orbit (MRI Picture, Figure 3). On 7/28/2011 he underwent endoscopic transnasal transsphenoidal resection of the sinonasal and sellar mass. He also had an enhancing lesion in the ethmoid sinus. He was recommended to have a

**Path Slide 1**

First operation A-E. A. Inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes (Hematoxylin and Eosin, 200X). B. High magnification (Hematoxylin and Eosin, 1000X) demonstrates a typical Rosai-Dorfman histiocyte with neutrophils and plasma cells undergoing emperipolesis (arrowed). C,D. The histiocytes are strongly immunoreactive for CD163 (200X) and S-100 (200X) respectively. E. High magnification (1000X) confirms the presence of emperipolesis (arrowed) within S-100 immunoreactive histiocytes. F. Second operation, sheets of foamy macrophages without emperipolesis (H&E, 400X). mass lesions

procedure for tissue diagnosis but he failed to do so and was lost to follow up.

The lesion consisted of an inflammatory infiltrate composed of lymphocytes, plasma cells and histiocytes (path slide 1A). High magnification images demonstrated intact inflammatory cells within the cytoplasm of many of the large histiocytes (path slide 1B). This phenomenon, known as emperipolesis, is

characteristic of Rosai-Dorfman Disease. These histiocytes were immunohistochemically positive for macrophage markers CD68 and CD163 (path slide 1C) as well as S-100 (path slide 1D, E), but were negative for CD1a. This immunophenotype is typical of Rosai-Dorfman histiocytes. In contrast, macrophages and Erdheim-Chester histiocytes are immunoreactive for CD68 and CD163

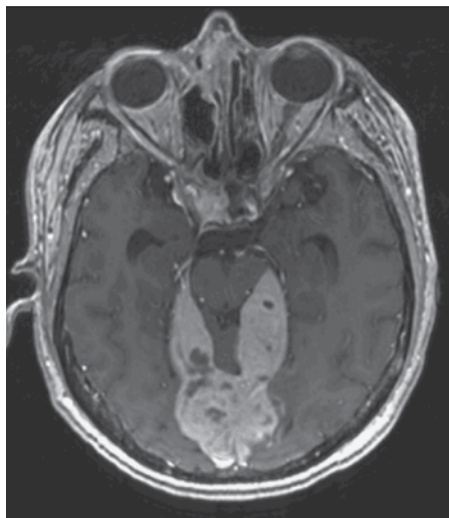


Figure 4
Pre Op MRI Brain Axial Image with Gadolinium 5/19/2012 – showing infratentorial and supratentorial mass

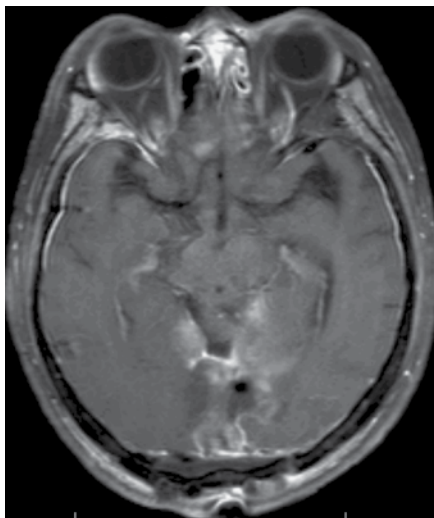


Figure 5
Post Op MRI Brain Axial Image with Gadolinium 5/26/2012 – showing gross total resection

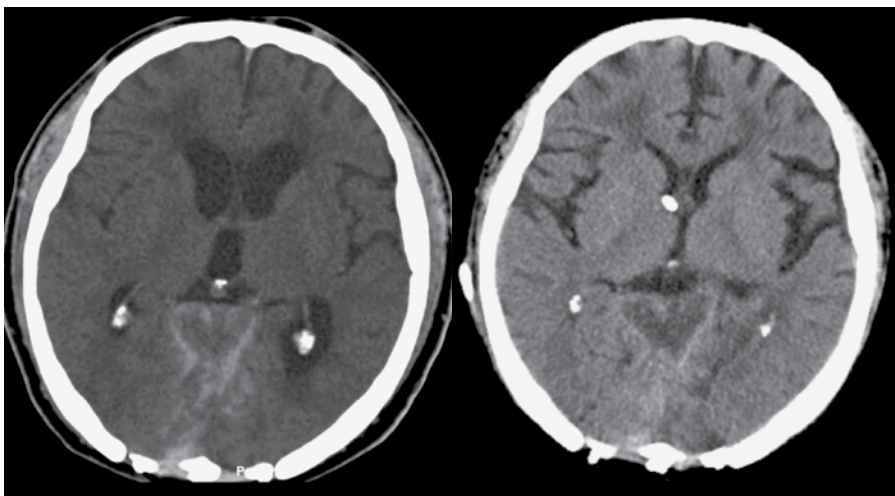


Figure 6
CT head without contrast 9/26/2014- showing hydrocephalus
CT head without contrast 10/04/2014 – post op after VP shunt showing resolution of hydrocephalus

but negative for S-100 and CD1a. Langerhan's cell histiocytes are immunoreactive for CD68, CD163, S-100, and CD1a. While the resection's pathology was consistent with RDD, the chest, abdomen and pelvis

done to rule out systemic disease showed pulmonary interstitial thickening with fibrotic changes and the perinephric fat stranding consistent with ECD.

During the same hospitalization he developed left ureteropelvic junction obstruction and hydronephrosis requiring stent placement.

He was discharged to rehab with outpatient follow up. From 8/29/2011 to 9/14/2011 he completed radiation therapy of 24 Gy in 12 fractions to the paranasal sinuses and whole brain. In December 2011 he was started on interferon alpha and had vast improvement of his symptoms.

In May 2012 he was readmitted with worsening headache and vision, on exam he had left homonymous hemianopia. MRI of the brain showed progression of the tentorial mass, compressing the occipital lobes bilaterally (MRI Picture, Figure 4). He was taken to the operating room and underwent an occipital/suboccipital craniotomy. A near total resection of a solid avascular mass arising from the tentorium was performed using a combined supratentorial and infratentorial approach. Post-operative MRI of the brain confirmed minimal residual on the right aspect of the tentorium and posterior falx (MRI Picture Figure 5).

Pathology from this resection was characteristic of ECD, revealing large numbers of foamy macrophages (path slide 1F) with foci of necrosis and cholesterol clefts. There was no evidence of emperipolesis and these macrophages/histiocytes were immunoreactive for CD68 and CD163, but negative for S-100 and CD1a. This immunophenotype is distinctly different from the original resection, and with the patient's clinical picture and multisystem involvement, points towards ECD. His headaches improved, and he was subsequently discharged home.

On June 12, 2012 he was admitted with an episode of unresponsiveness and was found to have a MRSA pneumonia with presumed sepsis. In the course of this hospitalization he was found unresponsive and in ventricular fibrillation. A cardiac catheterization revealed non-occlusive coronary artery disease and he underwent implantable cardioverter-defibrillator placement on 6/27/12.

By June 2013 his diabetes insipidus had resolved and overall he was feeling much better. He was lost to follow up since he returned to Mexico, however he presented in September 2014 with headache, gait

ataxia (right greater than left cerebellar dysmetria), left homonymous hemianopsia and on non-contrast head CT was found to have progressive communicating hydrocephalus. On 9/29/2014 he underwent a right ventriculoperitoneal shunt placement for relief (CT head pre and post VP shunt, Figure 6). CT head with contrast showed some recurrence of the tentorial mass (CT head with contrast, Figure 7) He recovered well enough and was discharged to rehabilitation unit.

DISCUSSION

ECD is a rare systemic non-LCH involving xanthogranulomatous infiltration of tissues by foamy histiocytes (lipid-laden macrophages) surrounded by fibrosis.² It is typically diagnosed in the fifth decade of life, with a mean age of 55, and is more prevalent in males than females. ECD is considered to be both a neoplastic and inflammatory disorder, as the disease associates with a specific oncogenic alteration in the form of the BRAFV600E mutation, as well as a characteristic inflammatory pattern of cytokines and chemokines.⁷

Although it is a clinically heterogeneous disease involving several organ systems, ECD patients most commonly present with bilateral osteosclerosis of long bones of the upper and lower extremities on CT scans.⁸ Other associated systemic manifestations include pseudotumor of the right heart, pericardial fibrosis, "hairy kidney" due to infiltration into perinephric soft tissue, exophthalmos, pulmonary fibrosis, and CNS involvement.^{2,9} Less than 50% of patients with proven ECD have neurologic involvement.⁸ The most common neurological symptoms are diabetes insipidus and cerebellar issues, both of which are part of our patient's history.¹⁰ Lesions in the CNS have been specifically identified in the hypothalamic-pituitary axis, cavernous sinus, orbits, paranasal sinuses, brainstem, and vertebral column.⁸ The prognosis for patients with ECD is variable and depends on the extent of disease.^{2,8} Renal failure, cardiomyopathy, and respiratory failure are the most common causes of death in patients with ECD.⁸ 59% of patients succumb to ECD after a mean follow-up of 32 months.¹¹

The definitive diagnosis for ECD can only be made via histopathology analysis and immunohistochemistry, with the presence



Figure 7

CT head with contrast 10/09/2014 – showing recurrence of infratentorial and supratentorial mass lesions

of infiltrating foamy, lipid-laden histiocytes, characteristic multinucleated Touton-type giant cells, and fibrosis.^{2,10} Cells are positive for CD68 and negative for CD1a.¹²

RDD is a nonmalignant non-LCH histiocytosis in which histiocytes infiltrate lymph nodes or extranodal tissues. RDD is typically diagnosed in the second or third decade of life and is more prevalent in African American individuals and in males compared to females.^{5,13} Patients with RDD classically present with symptoms of fever and massive, nonpainful cervical lymphadenopathy. Some patients experience night sweats and weight loss as well as painless maculopapular eruptions.^{5,14} Osteolytic bone lesions are rare in RDD, unlike in patients with Langerhans cell histiocytosis.¹⁵ 20% of patients with RDD have spontaneous regression without treatment.¹⁶ In patients without treatment, 70% will experience a relapsing and remitting course.¹⁶

Common sites for extranodal infiltration include the CNS, skin, orbit and eyelid, upper respiratory tract, and the gastrointestinal tract; some reports suggest extranodal involvement may occur in up to 40% of cases.⁵ CNS involvement of RDD is commonly with dura-based, extra-axial involvement of the cranium; spinal cord and intracerebral disease

are rare. Headaches and seizures are common as well as other neurological symptoms depending on the location of the lesion; constitutional symptoms are usually absent.⁵

To make a diagnosis of RDD, an excisional biopsy should be performed for immunohistochemical and morphological analyses.⁵ The hallmark of RDD cells is emperipolesis or the nondestructive phagocytosis of lymphocytes or erythrocytes.⁵ Cells will be positive for CD68 (KP-1), CD163, and S100 and are negative for CD1a.⁵

It is not uncommon for patients to present with both ECD and another form of LCH or non-LCH, as evidenced in 15% of 101 patients by Haroche et al.² Our patient presented in this case report falls into this category, concurrently expressing two systemic forms, ECD and RDD.

Treatment, both surgical and non-surgical, is similar for these two non-LCH diseases. For asymptomatic patients, it is recommended to observe, with close following of the disease for progression. However, for symptomatic patients with localized lesions, particularly in the CNS, surgical resection and/or radiotherapy is the treatment of choice. In a study involving 10 RDD patients with CNS involvement, 7 of them achieved remission at follow-up after surgical resection of the lesions.¹⁷

Interferon alpha (IFN α) therapy is the most studied,⁷ and Haroche et al. recommends IFN α therapy as the initial treatment for patients with symptomatic ECD. In their survival analysis of 53 patients, treatment with IFN α was an independent predictor of survival.² High dose IFN α is most effective for CNS and cardiac involvement as Haroche et al. reported symptoms did not resolve in response to low dose IFN α . Side effects of IFN α can be intolerable and include fatigue and depression.² Other non-surgical treatments currently being investigated for ECD patients with a more disseminated disease including: methotrexate¹⁸, canakinumab¹⁹, vemurafenib (20), and interleukin-1 targeting drugs/glucocorticoids.²¹ Vemurafenib, a BRAF inhibitor, has recently been utilized as an effective treatment for ECD patients harboring the BRAFV600E mutation with severe and refractory ECD, resulting in significant clinical improvement.^{2,7}

Patients with RDD experiencing symptoms have nonsurgical treatment options such as radiotherapy, steroids or chemotherapy agents including vinca alkaloids and anthracyclines.⁵ ECD and RDD are rare diseases and treatment options need to be studied further in randomized controlled trials in order to determine the best treatment for these patients.

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