

## An Unusual Cause of Central Diabetes Insipidus in a Young Female

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### Abstract

Central Diabetes Insipidus (CDI) in adults is most commonly occurs as a result of hypothalamo-pituitary surgery, head injury or various inflammatory and infiltrative disorders. CDI with mass lesions in the sellar-suprasellar area occurs due to infiltrative disorders like lymphoma, Langerhan's cell histiocytosis, and inflammatory disorders like hypophysitis, mass lesions like germinoma, craniopharyngioma and even metastases. Treatment and correct diagnosis depends on histopathology. Rosai-Dorfman Disease (RDD) is a rare disorder of unknown etiology characterized by abnormal proliferation of histiocytes. Extra nodal involvement is found in 40-50% of cases; with Central nervous system (CNS) involvement being uncommon hence in majority of instances intracranial disease is not suspected. Due to paucity of the reported cases, optimal treatment options are not known. We report a young female who presented with CDI, hyperprolactinemia and other features of hypopituitarism along with systemic manifestations including nodal and skeletal involvement. The patient was treated with combination of surgical debulking followed by oral glucocorticoid for 6 months with gratifying results.

**Keywords:** Rosai-dorfman disease; Sellar-suprasellar mass; Diabetes insipidus.

### Introduction

Central diabetes insipidus (CDI) is usually caused by damage to posterior pituitary gland, stalk or hypothalamus with most common causes in adults being pituitary surgery, traumatic brain injury, and infective, inflammatory or infiltrative diseases in the sellar region such as meningitis, tuberculosis, hypophysitis, sarcoidosis, lymphoma, langerhans cell histiocytosis. Benign histiocytic proliferation and infiltration of hypothalamo-pituitary area as an etiology of CDI is uncommon.

Rosai-Dorfman disease (RDD) or Sinus Histiocytosis with Massive Lymphadenopathy (SHML) was first described in 1969 by two pathologists Juan Rosai and Ronald Dorfman [1]. It is a benign, idiopathic histiocyte proliferative disorder with systemic symptoms such as fever, generalized weakness, fatigue, lymphadenopathy and pathognomonic histological and immuno-histochemical characteristics. RDD is equally prevalent in males and females [2] but central nervous system involvement though rare, occurs twice as common in males. RDD presenting as sellar-suprasellar mass is extremely rare with only few cases mentioned in the literature [2-8]. Here we report a case of RDD presenting as suprasellar mass causing CDI, hypopituitarism with hyperprolactinemia.

### Case Report

A 32 year-old- female presented to our institute with secondary amenorrhoea, polyuria, polydipsia and weakness for 9 years, with galactorrhoea, headache, and irritability for the last four years. She had a significant weight gain of 40 kg in past 6 months. There was no family history of any lympho-proliferative disorder, malignancy or immunodeficiency syndrome. Before coming to us, a primary care physician prescribed her levothyroxine 100 mcg, cabergoline 0.5 mg once a week and combined estrogen and progesterone pills for 5 months, on basis of her clinical picture and hormonal profile. As her condition remained statusquo, she stopped all medicines 4 months before being admitted with us, except for levothyroxine which she restarted from last 15 days.

The patient was obese (BMI-40.8 kg/m<sup>2</sup>), normotensive with no palpable lymphadenopathy or hepatosplenomegaly. Her routine investigations were normal except for hypercholesterolemia (269 mg/dl, 160-200) and hypertriglyceridemia (344 mg/dl, 100-150). Hormonal investigation revealed LH <0.1 mIU/ml ( 2.4-12.6), FSH 0.518 mIU/ml (1.5-1.5), testosterone 0.095 nmol/L ( 0.2-2.9), estradiol 39.5 pg/ml (12.5-166), ACTH 4.33 pg/ml (5-60), prolactin 64.8 ng/ml (4.79-23.3), iPTH 23.22 pg/ml (15-65), morning cortisol 301 nmol/L ( 171-536), T<sub>3</sub> 1.34 ng/ml (0.8-2.0), T<sub>4</sub> 12.28 µg/dl (4.8-12.7), TSH 0.018 µIU/ml (0.27-4.2). The baseline urine and serum osmolality were 59 mOsmol/kg (150-700) and 304 mOsmol/kg (275-290), respectively. With water deprivation, urine osmolality rose to 149.78 mOsmol/kg following administration of aqueous vasopressin (5 U s/c), suggestive of CDI. In the light of aforementioned investigations, she was started on oral desmopressin (100 mcg/day) and levothyroxine (100 mcg/day), following which she obtained relief.

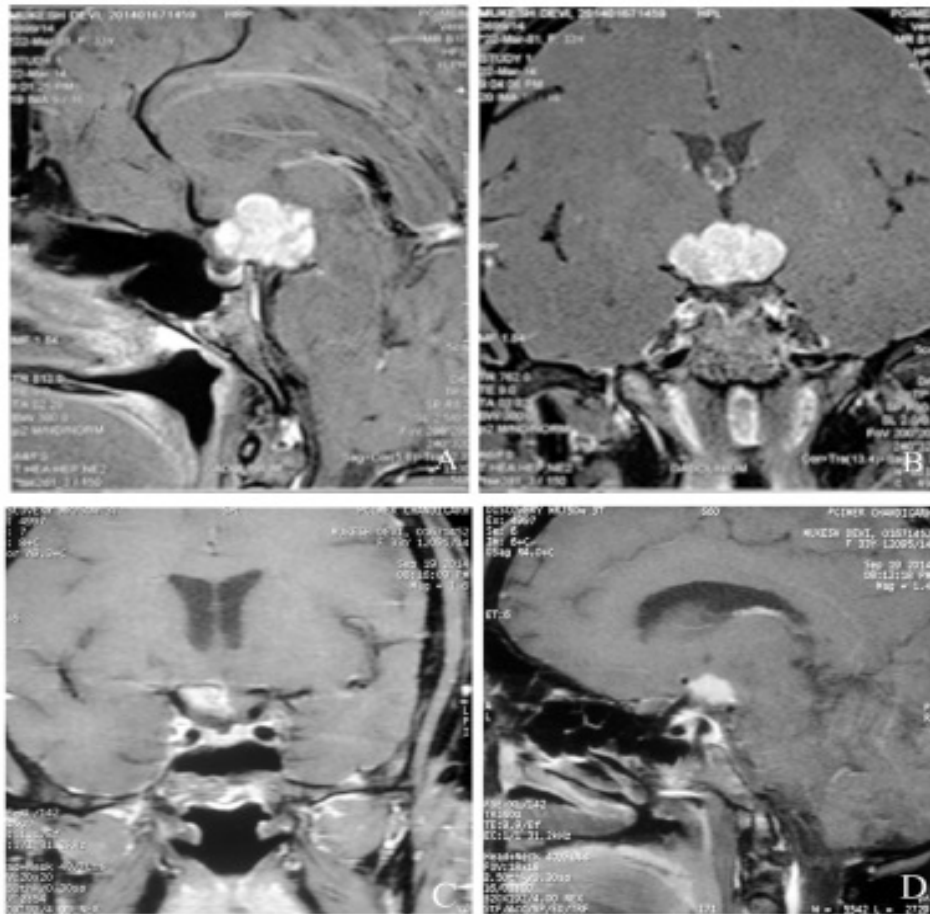
As a part of imaging studies, gadolinium enhanced MRI of brain showed a T1 hypointense, T2/FLAIR mildly hyperintense, lobulated mass in suprasellar region, measuring 2.8×2.5×1.8 cms, with homogeneous enhancement post-contrast. The mass was abutting the optic chiasma and left cavernous sinus, with pituitary stalk not separately visible (Figure 1A and 1B). Fluoro deoxy glucose positron emission computed tomography (FDG PET-CT) (Figure 2A and 2B) was done that revealed FDG avid suprasellar soft tissue mass (standard uptake value max. 37.7), multiple cervical level II, peri-pancreatic, portocaval,

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**Figure 1:** (A) T1 weighted non-contrast MRI shows hypointense lobulated mass measuring 2.8x2.5x1.8 cms. Superiorly it is reaching till anteroinferior aspect of 3<sup>rd</sup> ventricle, but no evidence of ventricular dilatation. (B) Homogenous enhancement following contrast administration. (C, D) Coronal and sagittal MRI of hypothalamo-pituitary area at one year of follow up shows small residual lesion.

precaval, paraortic and mesenteric lymph nodes along with lytic lesions in 7<sup>th</sup> cervical spine, bilateral humeri, scapulae, dorso-lumbar spine, sacrum, pelvic bones and faintly avid ground glass opacities (GGOs) in both lung fields (Figure 2C).

High Resolution Computed Tomography (HRCT) reconfirmed diffuse areas of GGOs and multiple tiny cysts in bilateral lung fields, with provisional diagnosis of lymphangioleiomyomatosis. In view of clinical symptomatology and a multisystem involvement, evaluation was done on lines of granulomatous etiology, but workup for tuberculosis and sarcoidosis was negative; hence first possibility of Langerhans cell histiocytosis was kept. Alpha Fetoprotein (AFP) levels,  $\beta$ hCG levels, and malignant cytology of Cerebrospinal Fluid (CSF) were non-contributory. She underwent a stereotactic biopsy from suprasellar mass which was inconclusive, thus was subjected to right pterional craniotomy with attempted gross total excision of mass. Grossly the mass was greyish pink and adherent to adjacent structures. The histopathology report came as a surprise, revealing sheets of macrophages with interspersed lymphocytes and some macrophages showing emperipolesis (cell within cell), few multinucleated giant cells with surrounding areas of extensive necrosis. On immune staining, the macrophages showed strong positivity for CD68 and negativity for CD1a, which is highly suggestive of RDD (Figure 3A-D).

After the diagnosis, patient was started on oral prednisolone at 60

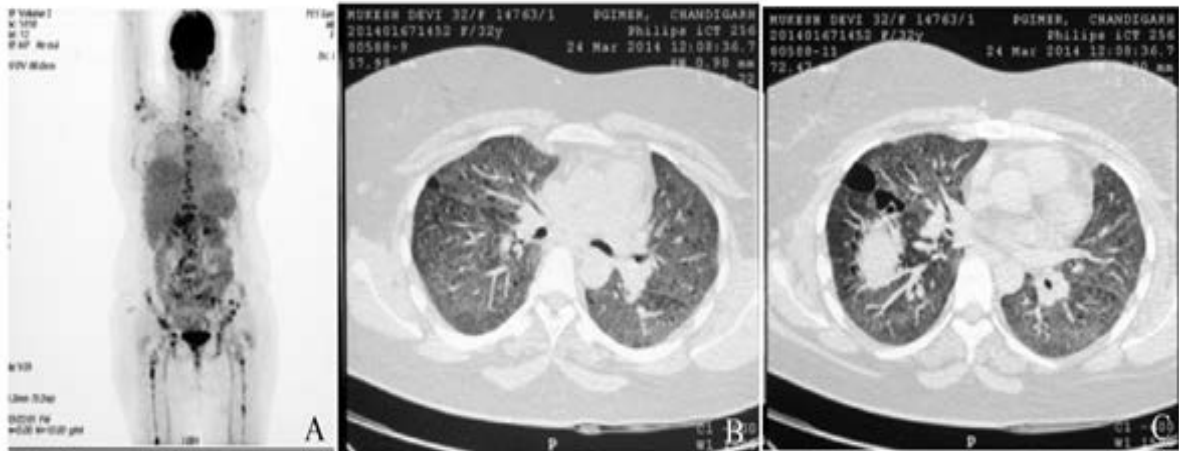
mg/day followed by tapering, after 6 weeks of therapy. At present she is on 5 mg of maintenance dose of prednisolone. She is symptom free after one year of follow-up, though hormone supplementation continues and imaging is showing small residue (Figure 1D) for which gamma knife surgery is planned.

## Discussion

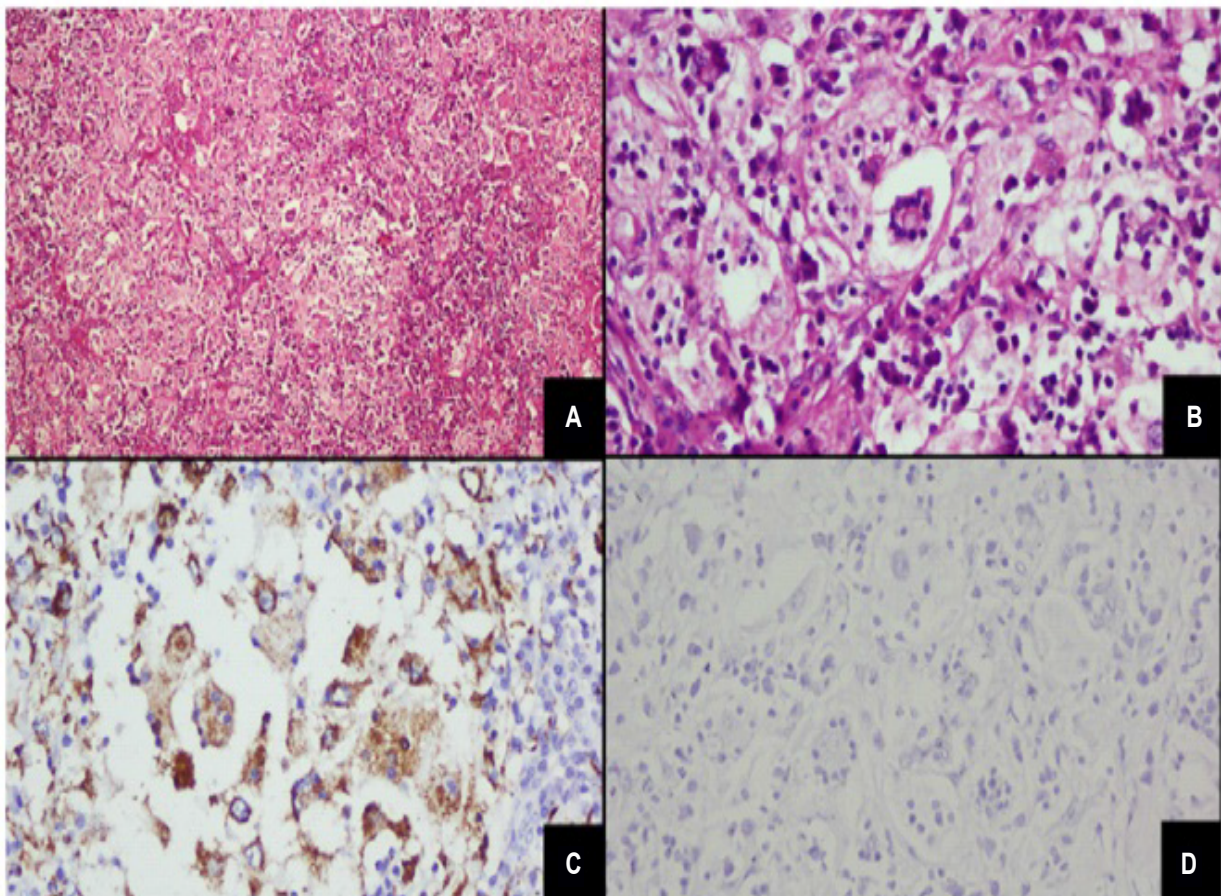
RDD is a rare disorder involving the lympho-reticular system however, 40% of cases can have extra nodal involvement with or without nodal disease. The extra-nodal involvement can be diverse [9-11] including naso-pharynx, paranasal sinuses, thyroid, orbit, skin and gastro intestinal tract. After extensive review of literature we came across 126 cases of central nervous system (CNS) RDD with incidence of 5% in small case series [10,12-14]. RDD of CNS was misdiagnosed in the past as plasma cell granuloma or inflammatory pseudotumor, and out of the 10 cases of CNS RDD at our center in last 20 years, this is the only case involving sellar-suprasellar area, while remaining had dura based mass (5), parenchymal lesions (3) and meningo-encephalitis like presentation (1).

RDD of CNS commonly presents as dura based lesion mimicking meningioma in more than 90% of cases reported. Two third of these cases have isolated intracranial disease [10,15-18] with involvement of sellar-suprasellar area being present only in 7 reported cases [Table1].





**Figure 2:** (A) FDG PET-CT showing intense tracer uptake in left level 1b cervical lymph nodes, measuring 1.3x1.2 cms, subcentrimetric nodes in cervical region, mediastinum and abdomen. (B) Intense FDG uptake with lytic-sclerotic changes in C7 vertebra, sternum, head and proximal shaft of both humeri, multiple ribs on left side, dorsolumbar vertebrae, pelvis and femur. (C) HRCT chest shows multiple discrete mediastinal lymph nodes. Note is made of multiple tiny cysts diffusely scattered in bilateral lung fields.



**Figure 3:** A (H&E; 100x)—Shows polymorphous infiltrate of cells which are predominantly histiocytes with abundant pale eosinophilic cytoplasm admixed with numerous plasma cells and lymphocytes. B (H&E; 400x)—The histiocytes exhibit emperipolesis wherein intact lymphocytes and plasma cells are present within the cytoplasm (Arrows). C (CD68 immunostain; 400x)—The Histiocytes show diffuse strong cytoplasmic positivity whereas the plasma cells and the lymphocytes present within the cytoplasm remain unstained thereby highlighting emperipolesis better (Arrows with oval ends). D (CD1a immunostain; 400x)—There is complete absence of staining in the histiocytes indicating that they are non-Langerhan's cell phenotype (Dotted arrows).

S.No.	Age / Gender	Reference	Sign & Symptoms	MRI Finding	Endocrine Dysfunctions Dysfunctions	DI	Treatment	Effect of treatment	Out Comes
1	32/ F	Dutta et.al. (present case)	CDI, Hypopituitarism, hyperprolactinemia, normal vision	Suprasellar mass of size 2.8×2.5×1.9 cm, T1-hypointense, T2/flair-mildly hyperintense, homogenous contrast enhancement	TSH, ACTH, Gonadotropin, GH, ADH deficiency	Y	Surgical debulking followed by tapering dose of oral prednisolone	Good response, mass remarkably decreased in size	Surviving at 1 year of follow up, hypopituitarism persisted
2	44/F	Kutlubay et al. 2014	CDI, Xanthelasma like skin lesion, lymph adenopathy,	Not known	Not known	Y	Systemic methyl prednisolone	Cutaneous disease under control	Not known
3	27 /M	Wang et al. 2011	CDI, vision loss, hypopituitarism	Sellar-supra sellar mass with anterior cranial extension, brightly enhancing on contrast		Y	Sub frontal – sphenoid surgery with gross total resection	Massive recurrence, CDI recurred after 3.7 years, received 50 Gy fractionated RT and intermittent prednisolone	Disease free at 5 years of follow up, hypopituitarism persisted
4	10/F	Wang et al. 2011	CDI, Hypopituitarism, normal vision, no palpable lymphadenopathy	Sellar mass	TSH, GH, ACTH deficiency	Y	Transphenoidal resection followed by 20 Gy fractionated RT	Multiple intracranial recurrences	Prednisolone 5 mg twice daily for 5 years, CDI improved, no recurrence, hypopituitarism persisted
5	63/F	Rotondo et al. 2010	Ataxia, diarrhoea, weight loss, abdominal pain	Only documented dural thickening, GIT infiltration	Normal cortisol and TSH	N	NA	Death due to sepsis, Autopsy- Neurohypophysis involvement by RD, Pituitary gland showed only lactotroph hyperplasia	Death
6	43/M	Wan et al. 2008	Vision loss left eye, bitemporal hemianopia, headache, no lymphadenopathy	Not mentioned	Suprasellar solid mass 3×3×2.5 cm, encasing optic chiasma, iso-intense on T1 and T2, heterogenous contrast enhancement, pre-operative diagnosis-meningioma,	N	Transphenoidal surgery-right posterior clinoid mass	Vision improved at 3 months of follow up	Repeated MRI did not revealed recurrence
6	15/F	Woodcock et al. 1999	Amenorrhoea initially, headache, blurred vision, mild papilledema	Enlargement of pituitary infundibulum with extension of soft tissue into the suprasellar cistern	Hypothyroidism	N	Mild interval increase in size	Biopsy; steroids	9 months alive
7	45/F	Kelly et al. 1999	Fever, Headaches, collapse, diplopia, hypernatremia, polyuria, and thirst	Suprasellar lesion sized 2 cm in diameter, arising from the posterior pituitary.	Hypopituitarism with low cortisol, thyroxine and gonadotrophins	Y	Diminished in size	Surgery; radiation; DDAPV, Chemotherapy; prednisolone	3 years alive
8	22/M	Ng. H.1995	Polyuria and polydipsia, obese, lacked secondary sexual characteristics and libido	Posterior pituitary 1.2 cm in diameter, extending from the tuber cinerium to the posterior portion of the pituitary fossa	Mild hyperprolactinemia, depressed testosterone, subnormal GH and cortisol	Y	NA	Biopsy; DDAPV	NA

ACTH: Adrenocorticotropic hormone; DI: Diabetes insipidus; DDAPV: Arginine vasopressin; GH: Growth hormone; TSH: Thyroxine stimulating hormone; Y: Yes/present; N: No/not present; NA: Information not available

**Table 1:** Summary of cases with Rosai–dorfman disease involving sellar-suprasellar area.

Out of the 126 cases of RDD with CNS involvement in the literature, only 5 had CDI. Other features of CNS RDD can be due to hypothalamic involvement and mass effects of tumor leading to galactorrhoea, memory loss, amenorrhoea, headache, seizures and neurodeficits. Lymph node involvement in CNS RDD is present in less than one third of cases, which may not be clinically evident as in our index case there were no clinically palpable lymph nodes but F18FDG PET scan revealed generalized lymph node involvement. In the index case, the nodes were small in size, a rarity in RDD [19], in agreement with one of the two cases described by Wang et al with sellar involvement, but non-palpable lymph nodes [3].

Moreover, in our patient multiple generalized lytic bone lesions were detected by FDG-PET scan that were not seen on conventional radiography, thus FDG PET CT can be used as a modality to find out areas of sub clinical involvement and disease burden, prior to treatment [20]. Our case also had hyperprolactinemia, which was possibly due to stalk compression as shown on gadolinium enhanced MRI, where stalk was not separately visible from the suprasellar mass.

The differential diagnosis of CDI with sellar-suprasellar mass encompasses infectious, granulomatous as well as neoplastic causes like tuberculosis, sarcoidosis, histiocytosis X, germinoma, craniopharyngioma or even metastases. Before MRI imaging, even we



kept a diagnosis of hypophysitis, with most probable causes being kept as tuberculosis or sarcoidosis as per our country's scenario. Gadolinium enhanced MRI of brain showed a T1 hypointense, T2/FLAIR mildly hyperintense, lobulated mass in suprasellar region, with homogeneous enhancement post-contrast, similar to previous reports of RDD [5,21,22]. In view of mass lesion, the patient was subjected to surgery for tissue diagnosis. The histopathology came as surprise to us and it completely changed the treatment.

Definitive diagnosis primarily relies on characteristic histopathology and immunohistochemistry of biopsy tissue. As for our patient, histopathology report taught us a lesson that proper biopsy should be decisive in planning further course of management. In the absence of signs of raised intracranial tension, the case could have been managed conservatively, as might have been the possibility with 7 previously described cases involving sellar-suprasellar area (6 were diagnosed on surgical specimen and one at autopsy). In terms of cytology, there were variable numbers of histiocytes intermixed with plasma cells, lymphocytes, and presence of emperipolesis (lymphocytophagocytosis), the characteristic finding in nodal disease, which is often less apparent in extra-nodal sites, however 6 out of 8 cases summarized by us showed this features, including our patient [2-8]. Immunostaining showed positivity for CD68, S100 and negativity for CD1a in all the cases including ours (Figure 3 A-D). Finding of polyclonal plasma cells, absence of acid fast bacilli and fungi, negativity for alpha-1 anti-chymotrypsin, alpha-1 anti-trypsin, CD15 and CD30 excluded other conditions [23,24].

Extensive review of all cases of RDD showed 70% had stable disease and 20% showed lasting remission without any treatment. Overall there were 21 deaths with 4 dying directly as a result of the disease. However, as CNS RDD is a potentially fatal immune dysregulation syndrome, more often than not it requires treatment [10], with surgery or steroids, chemotherapeutic agents, and radiation. Few case series has used only surgery as mode of treatment with good outcome [10,11,22,24]. Our patient was started on steroid therapy (Prednisolone) 60 mg/day after excision of the suprasellar mass followed by tapering of steroids after six weeks. Consequently, the mass reduced in size, but CDI is still persistent requiring desmopressin. With multiple modalities of treatment, 7 out of 8 cases of sellar-suprasellar RDD had lasting remission, as we hope, should also be the case with our patient.

In conclusion, ours is the first case report, where extensive bone and lung involvement was found along with suprasellar mass presenting as hypopituitarism, hyperprolactinemia and CDI. This case illustrates the superiority of FDGPET over structural imaging to demonstrate precise extent of the disease, as well as the fact that all suprasellar masses might not need excision and can be managed conservatively. RDD should always be kept as a differential diagnosis of dura based, sellar-suprasellar mass with CDI with or without multi system involvement.

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