Multiple Sclerosis in the setting of Cushing's Disease

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ABSTRACT

Background:

Patients with Cushing's disease (CD) often experience disabling symptoms but the diagnosis may be delayed by failure to recognize the constellation of gradually developing symptoms. Some of these symptoms such as severe fatigue and weakness can also be seen with other conditions such as multiple sclerosis (MS), an autoimmune demyelinating disease affecting the brain and spinal cord. MS may be a steroid responsive disease. Failure to recognize MS in the setting of CD may lead to inappropriate treatment and worse prognosis. We report, for the first time, an unusual case of CD which masked MS leading to severe flare-up of MS once CD was treated and cortisol level decreased.

Clinical Case:

A 45-year-old woman presented to the Endocrinology clinic for follow up of CD. Ten years ago, she had a 50 lb weight gain following pregnancy. She was diagnosed with Polycystic Ovarian Disease (PCOD)and asked to pursue lifestyle changes for weight loss. She had progressive symptoms and developed hypertension, borderline diabetes, depression, and severe fatigue. Evaluation led to the diagnosis of CD: 24 hour urine cortisol of 116.3 mcg/24hr (Reference range 4-50 mcg), cortisol level following 1 mg overnight dexamethasone administration of 18.2 mcg/dl (normal <1.8 mcg/dl). She was found to have a pituitary microadenoma measuring 5 X 7 mm for which she underwent trans-sphenoidal resection. Surgical pathology showed tumor cells diffusely immune reactive for chromogranin and ACTH and focally positive for prolactin. Post-operative cortisol levels were indeterminate for cure at 21.5 mcg/dl and 8 mcg/dl. She was placed on steroids which were weaned off. Patient developed progressive gait abnormalities over 3 months, with difficulty climbing stairs to eventually being unable to complete activities of daily living. Evaluation by Neurology with MRI brain revealed new demyelinating disease, compatible with a diagnosis of MS. Patient was placed on intermittent IV steroid pulses for multiple MS, with relapsing and remitting disease. She then developed recurrence of her Cushing symptoms including weight gain, diabetes, HTN and fatigue. She was found to have recurrence of her CD and underwent a second trans-nasal trans-sphenoidal resection of pituitary tumor. Pathology showed tumor was strongly immunoreactive to chromogranin and ACTH. Patient continues to be symptomatic, and the co-existence of MS and CD present a management challenge.

Conclusion:

We report a rare case of MS co-existing with CD. MS was likely masked by CD and flared up when CD was treated. Periods of remission of MS with high dose steroids attested to the steroid responsiveness of the condition. We seek to heighten awareness about co-existing co-morbid conditions such as MS with CD so as to facilitate early diagnosis and improve clinical outcomes. To our knowledge, this is the first case in the literature reporting MS in the setting of CD.

CASE

HPI:A 45-year-old woman presented to the Endocrinology clinic for follow up of Cushing disease(CD). Clinical history as below:

- Diagnosed with Polycystic Ovarian Disease 10 years ago (PCOD) and asked to pursue lifestyle changes for weight loss.
- Went on to develop hypertension, borderline diabetes, depression, and severe fatigue, subsequently diagnosed with CD.
- Found to have a pituitary ACTH producing microadenoma measuring 5 X 7 mm (Figure1) for which she underwent uneventful trans-sphenoidal resection. Surgical pathology confirmed tumor cells diffusely immune reactive for chromogranin and ACTH and focally positive for prolactin.

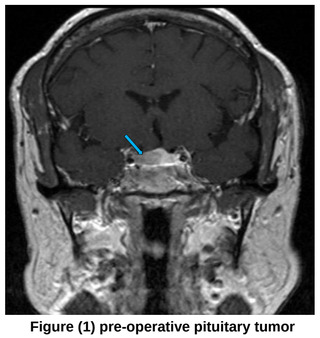


Figure (1) pre-operative pituitary tumor

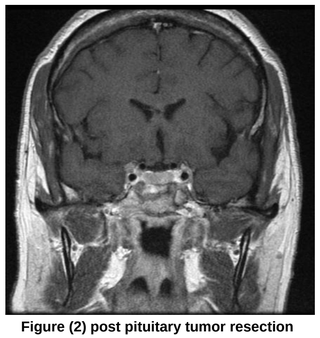
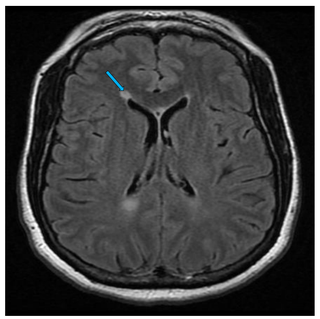


Figure (2) post pituitary tumor resection

- Post operatively (Figure2), she was on tapering steroid dose and then off.
- Developed progressive gait abnormalities over 3 months, right side numbness/weakness more than the left, reduced grip, with difficulty climbing stairs to eventually being unable to complete activities of daily living.
- Brain MRI demonstrated multiple areas of T2 hyperintense lesions primarily in the subcortical white matter, some that were radially oriented, in addition to three enhancing lesions of new demyelinating disease (Figure 3 and 4).

Variables	Results	References
24 hour urine free cortisol level	116.3 mcg/24hr	4-50 mcg/24hr
Serum cortisol post 1 mg overnight dexamethasone	18.2 mcg/dl	<1.8 mcg/dl
Postoperative serum cortisol	21.5 mcg/dl and 8 mcg/dl	4.0-22.0 mcg/dl
Serum cortisol following DMS test after recurrence	28 mcg/dl	4.0-22.0 mcg/dl
24 hour urine free cortisol Level after recurrence	66.2 mcg/24hr	4-50 mcg/24hr

CASE (cont.)



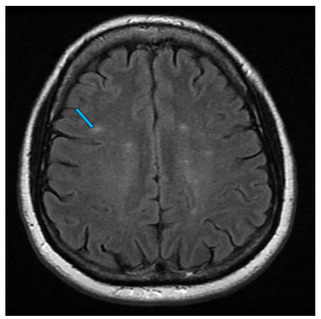


Figure (3) , Figure (4) new demyelinating disease

- Patient was placed on intermittent IV steroid pulses for multiple MS, with relapsing and remitting disease.
- Developed recurrence of her Cushing symptoms including weight gain, diabetes, HTN and fatigue, found to have recurrence of her CD (Figure 5 and 6).
- Patient underwent a second trans-nasal trans-sphenoidal resection of pituitary tumor.
- Pathology showed tumor was strongly immunoreactive to chromogranin and ACTH.

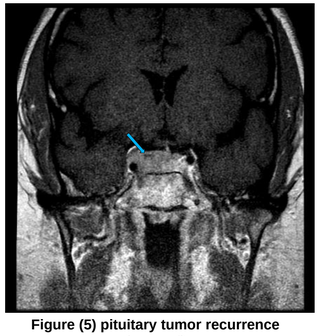


Figure (5) pituitary tumor recurrence (coronal)

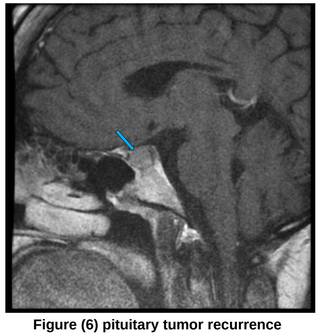


Figure (6) pituitary tumor recurrence (sagittal)

- Patient continues to be symptomatic, and the co-existence of MS and CD present a management challenge.

PE:

BP 143/74 mmHg | Pulse 103 b/m| Temp 36.7 °C (98 °F) | Ht 1.6 m (5' 3") | Wt 106.142 kg (234 lb) |Body mass index is 41.46 kg/m^2. Morbid obese lady in no distress. Mildly Cushingoid appearance. No pedal edema. No overt neurological deficits. Rest of the exam was within normal limits.

DISCUSSION

Cushing's disease is associated with clinical manifestations involving multiple organ systems, including musculoskeletal and immune systems.

Hypercortisolism induces reversible immunosuppression, and during active disease autoimmune disorders improve. Indeed, immunosuppression predisposing to infections is a major determinant of mortality in patients with Cushing's syndrome (CS), along with cardiovascular diseases[1]. Overt immune dysfunction after Cushing's syndrome remission has been reported, both new onset disease and exacerbation of pre-existing conditions (see table below). This phenomenon has been seen in both ACTH-dependent and independent cases; however a consecutive case series described all ACTH-dependent patients.

Immune dysfunction	CS etiology
Autoimmune thyroiditis (new onset)	Adrenal adenoma
Rheumatoid arthritis (exacerbation)	Pituitary adenoma
Celiac disease (exacerbation)	Pituitary adenoma
Sarcoidosis (new onset)	Adrenal adenoma
Systemic lupus erythematosus (new onset)	Pituitary adenoma
Seronegative arthritis (new onset)	Pituitary adenoma
Retinal vasculitis (new onset)	Pituitary adenoma
Graves disease (exacerbation)	Ectopic
Vitiligo, three cases (not specified)	Not specified
Sclerosing pancreatocholangitis (new onset)	Pituitary adenoma
Atopic dermatitis (exacerbation)	Adrenal adenoma
Psoriasis (exacerbation)	Pituitary adenoma
Autoimmune pemphigus (exacerbation)	Adrenal adenoma

Some postulated mechanisms:

Inhibition of production of IL-1 and IL-2 by activated T cells, indirectly affecting B cells as well Decreased ratio of CD4+/CD8+ lymphocytes. This is the first report of new onset multiple sclerosis reported after partial remission of Cushing's disease, to the best of our knowledge. Proximal muscle weakness has been described in up to 67% of patients with Cushing's syndrome. The muscle weakness in co-existing or newly developed MS as in our patient may be hard to distinguish from Cushing's disease. Clinicians should bear in mind the possibility of autoimmune diseases that follow remission from Cushing's disease so as to make the diagnosis in a timely manner.

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There is no conflict of interest disclosures