Multiple Sclerosis in the setting of Cushing’s Disease

Hiba Basheer MD, Sreevidya Subbarayan MD
Department of Internal Medicine, Division of Endocrinology, University of Florida, Gainesville, FL

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 challenge to diagnosis as symptoms may overlap with CD, and severe fatigue, subsequently diagnosed with CD.

CASE
HPLA 45-year-old woman presented to the Endocrinology clinic for follow up of Cushing disease. 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 × 7 mm (Figure 1) for which she underwent unsuccessful trans-sphenoidal resection. Surgical pathology confirmed tumor cells diffusely immune reactive for chromogranin and ACTH and focally positive for prolactin.

CASE (cont.)
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 diabetes, depression, and severe fatigue, subsequently diagnosed with CD.
- Patient underwent a second trans-nasal trans-sphenoidal resection of pituitary tumor.
- Pathology showed tumor was strongly immunoreactive for chromogranin and ACTH.

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 disease. Indeed, 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

<table>
<thead>
<tr>
<th>CS etiology</th>
<th>Immune dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune thyroiditis (new onset)</td>
<td>Adrenal adenoma</td>
</tr>
<tr>
<td>Rheumatoid arthritis (exacerbation)</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Celiac disease (exacerbation)</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Sarcoidosis (new onset)</td>
<td>Adrenal adenoma</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (new onset)</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Seronegative arthritis (new onset)</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Retinal vasculitis (new onset)</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Graves disease (exacerbation)</td>
<td>Ecotopic</td>
</tr>
<tr>
<td>Villigo, three cases (not specified)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Scleroding pancreatocholangitis (new onset)</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Aplastic dermatitis (exacerbation)</td>
<td>Adrenal adenoma</td>
</tr>
<tr>
<td>Transsudation (exacerbation)</td>
<td>Pituitary adenoma</td>
</tr>
<tr>
<td>Adrenal autoimmune pemphigus (exacerbation)</td>
<td>Adrenal adenoma</td>
</tr>
</tbody>
</table>

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+CD69 lymphocytes. This is the first report of new onset immune suppression reported after partial remission of Cushing’s disease, to the best of our knowledge.
- Proximal muscle weakness has been described in up to 57% 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.

REFERENCES

ABSTRACT
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/dl (Reference range 4-50 mcg/dl). Post operative cortisol levels was 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-sphenoidal resection of pituitary tumor. Pathology showed tumor was strongly immunoreactive for 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 normally in the setting of CD may reduce awareness of 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.

Figure (1) - Figure (4) new demyelinating disease

Figure (5) pituitary tumor recurrence (cortical)

Figure (6) pituitary tumor recurrence (sagittal)

Variables
24 hour urine free cortisol level
Serum cortisol post 1 mg overnight dexamethasone
Postoperative serum cortisol
Serum cortisol following DMS test after recurrence
24 hour urine free cortisol level

Results
116.3 mcg/24hr
18.2 mcg/dl
21.5 mcg/dl and 8 mcg/dl
28 mcg/dl
66.2 mcg/24hr

References
- Pathology
- Immunolocalization of chromogranin and ACTH and focally positive for prolactin.
- Patient presented with intermittent IV steroid pulses for multiple MS, with relapsing and remitting disease.
- 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 normally in the setting of CD may reduce awareness of 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.