Warning:
Side-Effects May Include
Upset-Stomach and
Psychosis

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Case Presentation

Case S.L.

- CC: Upper and lower eyelids swollen.
- HPI: 51 y/o female
  - "eye swelling" left > right X several months
  - Followed by outside Eye MD and treated for blepharitis
  - Recent Dx Graves Disease
  - Dx corneal ulcer 2 weeks ago by outside Eye MD \(\rightarrow\) Vigamox
  - Outside "thyroid specialist" started 60mg prednisone po 2 days
  - No pain with EOM. No light sensitivity
    - Brought by sister to MEEI EW for "second opinion"

PMHx

- DM2 (Hgb A1C 7.7)
- Recent diagnosis of Graves Disease
- Bipolar Disorder
- Hypertension

- Allergy: Haloperdidol
Medications

- Aspirin
- Ativan
- Risperdal
- Erythromycin ophthalmic ointment
- Fenofibrate
- Fosamax
- Methimazole
- Januvia
- Lamisil
- Metformin
- Metoprolol
- Perphenazine
- Zyrtec

FHx & SHx

- Lives independently, brother is health care proxy
- Smokes "6 cigarettes per day"

POHx

- No prior injuries or surgeries
EW

- Corneal Ulcer OD inferior, peripheral
- Fortified vancomycin and tobramycin initiated Q6H
- Scraped and cultured
- F/U next day EW and referred to cornea clinic

- Thyroid Orbitopathy left > right.
  - No APD, full color vision
  - Advised to F/u oculoplastic clinic ASAP
  - Lubrication

Oculoplastics Exam
3 days following initial EW visit

<table>
<thead>
<tr>
<th>V</th>
<th>T</th>
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<tbody>
<tr>
<td>20/25</td>
<td>17</td>
</tr>
<tr>
<td>20/30-</td>
<td>18</td>
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<tr>
<td>10/10</td>
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</table>

- Pupils: 4 ➔ 2 OU; No APD
- Orbits severe resist. to retropulsion OU
- MRD1: +3 OD, +2 OS
- Inferior Scleral Show: ~3mm OU
- Lagophthalmos 0 OD; 2mm OS
- Hertel Exophthalmometry: EOM: -1 upgaze and abduction OU
  - Base 94
  - OD 27
  - OS 28
SLE
L/L/A: some erythema / blepharitis
C/S: 1+ injection OU with 3+ inf chemosis OS, Swollen caruncle OS
J: 1mm X 1mm inf ulcer 8 o’clock OS, filaments sup
A/C: trace cell OD
I: Flat OU, WNL OU
L: Clear OU

DFE
• ON pink & sharp OU
• C/D: 0.4 OU
• Mac: Flat OU
• Vessels: WNL OU
• Vitreous: Clear OU
Plan

• Continue treatment for corneal ulcer – followed by Cornea service
• Frequent lubrication.
• Smoking cessation!
• Humphrey Visual Field test
• Continue 60mg of prednisone daily for active thyroid orbitopathy
  • With monitoring of blood glucose by PCP
• Follow-up Oculoplastics clinic 2 weeks

Moderate to severe Thyroid Eye Disease with optic neuropathy OS > OD

• Continue steroid therapy with close follow-up to monitor for improvement of optic neuropathy.
• Close following with PCP and endocrinologist.
• Smoking cessation!
2 weeks later

- Clinic follow-up
- Quit smoking – using transdermal nicotine patch
- Punctal plug by cornea service
- PCP initiated a steroid taper: glucose up to 400’s
- Notes increased swelling over past few days.
- Vision is “dirt”
- Orbits severe resist. to retraction OU
- EOM: 3 all directions OU
- Lagophthalmos: 5 OD; 7mm OS
- Hertel Exophthalmometry:
  - Base 99
  - OD 29
  - OS 28.5
Emergent Bilateral Orbital Decompression

Hospital Course

- Pulsed-dose IV Solumedrol (1 gram IV)
- Prednisone 60 mg po daily X 3 ➔ 50 mg po QDay
- By POD 1: VA 20/40 OU, Color 8/8 OU

DM2: Sliding scale insulin ➔ FS to 300-400's

POD 2 Mental Status: Disorganized, talking to self, hypomanic

- Different medications and insulin sliding scales:
  - Unable to control blood glucose adequately.

- Mental status further deteriorated:
  - Psychiatry Consultation ➔ Involuntary Admission to MGH
  - Likely steroid-induced hypomania / psychosis
  - Workup to rule-out metabolic delirium WNL
Dilemma

- Patient in severe acute inflammatory phase of TED.
  - Had successful decompression.
  - Post-operative orbital inflammation controlled with steroids.

- But…
  - Blood glucose uncontrolled with complicated insulin regimen.
  - Significant deterioration of mental status.

Dilemma

- Concern:
  - If steroids stopped or tapered too quickly.
    - Return of inflammation / congestion → vision loss.

So what can we do now?

Steroid-Sparing Options

- Orbital Radiotherapy
  - Delayed onset of action (~6 weeks)
  - Relatively contraindicated in this diabetic patient (retinopathy)
  - Literature unclear

- Immunomodulatory Therapy
  - E.g. rituximab
rituximab

- Human/Murine chimeric monoclonal antibody
- Binds to CD20 on B-lymphocytes
- Impairs antigen presentation
- Uses:
  - Non-Hodgkins Lymphoma 1997
  - Chronic Lymphocytic Leukemia
  - IgM-related polyneuropathies 1999
  - Rheumatoid Arthritis 2001
- Off-label use for thyroid orbitopathy beginning 2006
  - Given at lower Rheumatoid Arthritis-treatment dosage.
  - 1 gram IV Q week x 2


Case S.L.

- Underwent Rituximab infusion protocol with Rheumatology
  - No complications
- Prednisone tapered – off by POW 6
- Blood glucose: 100’s
- Released from inpatient psychiatry ward (after ~3 week stay).
  - Coherent, pleasant, happy

POW 6

V 20/30
CC
20/30
T 19
C 8/8
Corticosteroids & Psychiatric Side Effects

- Pathophysiology: NOT well understood

- Theories
  - Affects dopamine and acetylcholine pathways
  - Decreased levels of serotonin
  - Possible toxic effect on hippocampus

Corticosteroids

- Spectrum of psychological effects
  - Hypomania / mania
  - Depression
  - Mixed state
  - Anxiety / panic
  - Suicidality
  - Delirium
  - Aggressive behavior
Corticosteroids

- Boston Collaborate Drug Surveillance Program (BUMC)

"Acute adverse reactions to prednisone in relation to dosage."

- "psychiatric reactions"
  - 1.3% of 463 patients < 40 mg/day prednisone
  - 4.6% of 175 patients 41 to 80 mg/day
  - 18.4% of 38 patients > 80 mg/day

Steroid-Induced Psychiatric Syndromes

- Meta-Analysis: Lewis & Smith 1983
  - 14 cases from University of Iowa
  - 79 cases from literature
  - 29 studies of clinical efficacy of steroids for various conditions
  - 5.7% steroid-treated patients exhibited psychiatric manifestations
    - Depression 40.5%
    - Mania 23.9%
    - Depression/Mania 7.6%
    - Psychosis 13.9%
    - Delirium 10.1%
  - Average time to onset of symptoms: 11.5 days
    - 39% by 1 week of steroid treatment
    - 53% by 2 weeks

Steroid-Induced Psychiatric Syndromes

- Prospective Study: Neber et al 1996
  - 50 Ophthalmic Patients with uveitis, Munich, Germany
  - 8 days either methylprednisolone or fluocortolone
    - Equipotent, 1mg = 1.25 mg prednisone equivalent
    - Average dosages: 119mg t.i.d. 1st day, tapered 50mg/day 8th day
    - Psych & Cognitive function evaluated before and after treatment.
  - Results: 36% of patients developed DSM-III-R mood-disorder.
    - 13/50 (26%) Mania
    - 5/50 (10%) Depression
    - No relation to gender, history of psychiatric illness, Med Dx.


Steroid-Induced Psychiatric Syndromes

• Kenna et al, 2011, Stanford University Medical Center
• Review of 55 cases of steroid-induced psychiatric syndromes
  • 54.5% hypomania/mania (14 days, avg. dose 44.8 mg prednisone)
  • 23.6% clinical depression (12 days, avg. dose 73.2 mg prednisone)
  • 20% delirium (7 days, avg. dose 63.2 mg prednisone)
  • 61.8% psychotic (i.e. hallucinations and/or delusions)
  • 40% suicidal ideation (half of whom were psychotic)
  • 1 patient committed suicide
• Possible reporting bias of extreme cases

Graves Orbitopathy

• Graves Hyperthyroidism → 60% will develop orbitopathy.
  • 5 to 10% of patient with orbitopathy are euthyroid
  • <10% may be hypothyroid at presentation

• TSH receptor-stimulating autoantibody
  • TSH receptor is also present in orbital tissues / fibroblasts.
    → orbitopathy
    Fibroblasts produce excess glycosaminoglycans → edema.
    Preadipocytes differentiate to adipocytes → increased orbital fat.
  • Type 1 helper T cells, mast cells, B cells, plasma cells, histiocytes.

Graves Orbitopathy

• 40% signs of hyperthyroidism coincide with orbital signs.

• Orbitopathy can occur years following the diagnosis of Graves

• Significant orbitopathy → compressive optic neuropathy in 3 to 5%
**Clinical Activity Score (CAS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Painful, oppressive feeling on or behind globe.</td>
</tr>
<tr>
<td>II</td>
<td>Pain on attempted-up, side, or down gaze.</td>
</tr>
<tr>
<td>III</td>
<td>Bulge of the eyelids.</td>
</tr>
<tr>
<td>IV</td>
<td>Bulge of Conjonctiva.</td>
</tr>
<tr>
<td>V</td>
<td>Chemosis.</td>
</tr>
<tr>
<td>VI</td>
<td>Inflammation, Gland Swelling.</td>
</tr>
<tr>
<td>VII</td>
<td>Swelling of Caruncle or Plica.</td>
</tr>
</tbody>
</table>

Additional criteria:

- S: Increase in progress of more than 1 mm in two to three months.
- A: Decrease in Visual Acuity of one or more lines in one to three months.
- R: Increase in Eye Movements of more than 5 degrees in any direction in one to three months.

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**Management of TED**

- For all patients:
  - Aims to achieve euthyroid state (e.g. thyroid suppression therapy or methimazole).
  - **SMOKING CESSATION** decreases risk of developing Graves Ophthalmopathy.

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**Table 1.** Smoking behavior and outcome of mild Graves Ophthalmopathy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Non-smoker</th>
<th>Former Smoker</th>
<th>Current Smoker</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>10</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 2.** Smoking behavior and outcome of treatment of severe Graves Ophthalmopathy with orbital radiation therapy and high-dose immunosuppression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Response</td>
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<td>15</td>
<td>4</td>
</tr>
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**NO SPECS**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>No symptoms or signs</td>
</tr>
<tr>
<td>O</td>
<td>Only signs (e.g. lid retraction), no symptoms</td>
</tr>
<tr>
<td>S</td>
<td>Soft tissue involvement</td>
</tr>
<tr>
<td>P</td>
<td>Proptosis</td>
</tr>
<tr>
<td>E</td>
<td>Extraocular muscle involvement (mobility)</td>
</tr>
<tr>
<td>C</td>
<td>Conveal involvement</td>
</tr>
<tr>
<td>S</td>
<td>Sight loss (optic neuropathy)</td>
</tr>
</tbody>
</table>

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**References:**
- Reference 1: Reference text.
- Reference 2: Reference text.
Management of TED

- **Mild**
  - Artificial Tears
  - Tetracyclines
  - Regular monitoring: ~15% progress to moderate/severe

- **Moderate/Severe** (no threat to vision, but significant impact on daily life to justify immunosuppression)
  - Corticosteroids (oral vs. intravenous) 80% response rate

- **Severe/Compressive Optic Neuropathy/Corneal Breakdown**
  - High dose corticosteroids
  - If clinical deterioration \(\Rightarrow\) urgent orbital decompression

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IV Glucocorticoids

INTRAVENTOUS GLUCOCORTICOID

- Clinical Review: Zang et al 2011
  - 13 Non-randomized trials (346 patients)
  - 10 Randomized Trials (234 patients)
  - Overall response rate: 80%
  - Lower rate of adverse events compared to oral glucocorticoid:
    - 62.6% IV
    - 72.8% Oral
  - **Recommended 12-wk IV Pulsed Steroid as First-Line Treatment for active, moderate-to-severe USA**
    - 1800 mg IV methylprednisolone IV Q Week X 6 weeks
    - Then 750 mg IV methylprednisolone Q Week X 6 weeks
IV Glucocorticoids
Graves’ Orbitopathy

- IV Glucocorticoid Therapy for GO:
  - Morbidity 6.5%
  - Mortality 0.6%
  - Coronary thrombosis
  - Cerebral thrombosis
  - Acute hepatic failure

- Serious events occurred ONLY in patients who received greater than 500mg methylprednisolone daily or alternate day dosing.


Careful patient selection and monthly monitoring.

- Patients must be screened for:
  - Recent hepatitis
  - Liver dysfunction
  - Cardiovascular morbidity
  - Severe hypertension
  - Inadequately managed diabetes
  - Glaucoma

- Cumulative methylprednisolone dose should not exceed 8 grams.
- Dexamethasone should NOT be administered on consecutive days except in cases of severe threat to vision.


Active and Moderate to Severe Graves’ Orbitopathy

Contraindications:
- Recent hepatitis
- Liver dysfunction
- Cardiovascular morbidity
- Severe hypertension
- Inadequately managed diabetes
- Glaucoma

NO IV glucocorticoids

No contraindications

High-dose IV glucocorticoid pulses:
- Cumulative dose < 8 g
- Avoid administration on consecutive days
- Watch for hypertension
- Preferentially given as single dose 0.6 g/day

Monitoring warranted (monthly):
- Liver chemistry, glucose, blood pressure

Did our patient even need steroids after surgery?


- Reviewed 14 Studies
- Overall favorable outcomes 48% to 97%
- Definite Radiation Retinopathy 1% to 2% at 10 years
- Possible radiation retinopathy ~21%
- No secondary malignancies encountered
- In general, studies had heterogeneous populations
- Effect on proptosis, lid position, eyelid swelling not better than sham
- Beneficial effect on vertical ductions
- Patients with optic neuropathy were excluded from randomized trials.
rituximab

- Thyroid Associated Orbitopathy is considered T-cell mediated
- rituximab affects B-cells (CD-20)
- TAO patients treated with rituximab:
  - NO EFFECT on circulating autoantibodies
  - Mechanism of action thought to be interference with antigen-presenting function of B-cells

- Silkiss RZ, et al 2010
  - 12 TAO patients treated with RTX, Prospective
  - Significant improvements in CAS, 1 year follow-up.
  - 2 pts treated with glucocorticoids, tapering 1 month prior to RTX.
  - 2 patients required maintenance therapy (tapering prednisone for 1 to 2 months following RTX).
  - No adverse side effects from RTX infusion or at 1 year.

- Khanna D, et al 2010
  - 6 TAO patients unresponsive to glucocorticoids ➔ treated with RTX, Retrospective
  - CAS after RTX: 5.5 ➔ 1.3 average.
  - Remained quiescent (CAS 0.7) at ~6 month follow-up
  - No patients experienced disease relapse after RTX infusion.

Problems with literature / studies:

- Inhomogeneous patient populations
- Different lead-times of disease
- Some had received steroids previously or concurrently
- A few had undergone prior orbital radiotherapy
- No controls
- Natural history of TAO
  - i.e. eventually improves / stabilizes
## Conclusion

- The pathophysiology, categorization, and treatment of Thyroid Eye Disease can be complicated.
- Steroids are not a benign treatment.
- Steroid-sparing immunomodulatory therapy for the treatment of thyroid-associated orbitopathy is promising, although larger, controlled studies are indicated.

## References