Overview

I. Case

II. Odynophagia

III. Idiopathic Esophageal Ulcers

IV. Treatment of IEU: Review of Literature
Cc: dysphagia/odynophagia x 3 months

HPI: 34 yo M w/ PMH AIDS (CD4 ct 84 in 1/2014) and GERD, who had 3 months of dysphagia and odynophagia. He feels like solids are getting “stuck” in the mid-epigastric region, and has odynophagia with eating or drinking. Has c/o 35 lbs x 3 months 2/2 poor PO intake. Rare nausea or emesis.

Of note, had EGD 2 months ago at an outside hospital and reports it showed “ulcerations.” He was also treated for severe esophageal candidiasis (IV antifungal, then PO diflucon prescribed on 2 separate occasions).

ROS: Intermittent chills. No fevers, change in bowel habits, hematochezia or melena.
PMH: HIV/AIDS, oral and esophageal candidiasis, “ulcers,” GSW

PSx: none

All: NKDA

FH: non-contributory

SH: ½ ppd tobacco x 11 years, no alcohol, THC 2-3x daily

Meds: *recently re-started HAART 1 month ago. Was off HAART x 4 years. Atripla 1 tab daily, Bactrim DS 1 tab daily, fluconazole 100 daily, dicyclomine q12h, lansoprazole 15mg daily, ranitidine 150mg bid
PE:
VS: T96.7-97.3 degrees C, HR 89-106, RR 16-18, BP 110/60-130/85, 99-100% O2 sat

weight 110 lb, height 5’9” (BMI: 16.2 kg/m^2)

GEN – NAD, cachectic
HEENT – PERRRL, EOM I, anicteric, no oral thrush, no cervical LN
CV - +s1,s2; no M/R/G
CHEST – CTA B
Abd - +BS normal soft NT ND
Skin – small healed excoriations BLE, tattoos
Neuro - +5/5 strength x 4 extremities, normal sensation
Labs:
WBC 2.7: N82, L14, M3, E1
Hgb 13.2, MCV 88.1, RDW 12.1
Plt 690

Na 128, K 5.6, Cl 93, CO2 24

Tprot 8.9, Alb 3

Prealbumin 26.2

Ferritin 549.6
Blood cx x 2 neg
Acute hep panel neg
CMV IgM <0.2 (low), CMV IgG >8
Crypto Ag neg
Urine Histo Ag neg
EGD Findings:

Esophagus:
-Severe, circumferential LA grade D esophagitis from 27 cm to 37 cm.
-At least three esophageal nodules/polyps with a couple having overlying white, clean-based ulcers (1mm) located in proximal esophagus at 27 cm. One appears to be on a stalk.
-Possible inflammatory polyps. Less likely duplication cysts or fibrovascular polyps.
-1 long non-obstructive esophageal lesion with normal-appearing overlying mucosa. The lesion is approximately 5-10mm wide and extends from 30 cm to 37 cm. It is wider proximally and tapers distally. No stigmata of bleed or active bleeding. Lesion not biopsied as unclear if has underlying vasculature. Differential includes normal esophagus with surrounding severe ulceration, inflammatory polyp, less likely esophageal duplication.

Stomach:
-Moderate gastritis in antrum
-One 5mm white, clean-based ulcer at angularis, no stigmata of bleed or active bleed
Pathology:

**Proximal and Distal esophageal ulcer bx:**
- fragment of ulcer base with inflammatory exudates.
- fragments squamous mucosa, granulation tissue
* neg AFB and fungal stains
* neg CMV and HSV ½ stains

**Gastric bx:** mild chronic gastritis, neg H pylori
Treatment course:

Presumptive treatment for HSV and CMV while awaiting path from EGD, evaluate for CMV retinitis:

1. Micafungin 150 mg IV daily
2. Ganciclovir 5mg/kg IV q12 hours (CMV retinitis ruled out)

Reflux esophagitis – carafate and PPI bid

After outside EGD path report neg for viral/fungal etiology, started on treatment for **Aphthous esophagitis**

1. Prednisone 40 mg daily x 1 week, then tapered over 1 month (per ID note: no good trials but case reports)

GI recommendation: Repeat EGD with MAC 6 weeks ensure gastric ulcer healing
Odynophagia = painful swallowing, involves esophagus

- Dull retrosternal ache
- Stabbing pain radiates to back

- Inflammation involving mucosa OR muscle

- MCC
  1. Infectious esophagitis (immunocompromised)
  2. Caustic ingestion
  3. Radiation injury
  4. Pill-induced esophagitis
<table>
<thead>
<tr>
<th>Table 12-3 Causes of Odynophagia</th>
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<tbody>
<tr>
<td><strong>Caustic Ingestion</strong></td>
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<tr>
<td>Acid</td>
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<td>Alkali</td>
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<tr>
<td><strong>Pill-Induced Injury</strong></td>
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<tr>
<td>Alendronate and other bisphosphonates</td>
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<td>Aspirin and other NSAIDs</td>
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<tr>
<td>Emepronium bromide</td>
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<td>Iron preparations</td>
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<tr>
<td>Potassium chloride (especially slow-release form)</td>
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<tr>
<td>Quinidine</td>
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<tr>
<td>Tetracycline and its derivatives</td>
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<tr>
<td>Zidovudine</td>
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<tr>
<td><strong>Infectious Esophagitis</strong></td>
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<tr>
<td><strong>Viral</strong></td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Epstein-Barr virus</td>
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<tr>
<td>Herpes simplex virus</td>
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<tr>
<td>Human immunodeficiency virus</td>
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<tr>
<td><strong>Bacterial</strong></td>
</tr>
<tr>
<td>Mycobacteria (tuberculosis or <em>Mycobacterium avium</em> complex)</td>
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<tr>
<td><strong>Fungal</strong></td>
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<tr>
<td><em>Candida albicans</em></td>
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<tr>
<td>Histoplasmosis</td>
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<tr>
<td><em>Protozoan</em></td>
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<tr>
<td>Cryptosporidium</td>
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<tr>
<td><em>Pneumocystis</em></td>
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<tr>
<td><strong>Severe Reflux Esophagitis</strong></td>
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<td><strong>Esophageal Carcinoma</strong></td>
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</table>

NSAIDs, nonsteroidal anti-inflammatory drugs.
Esophageal Disease in HIV

- 50-70% Candida albicans
- 15-35% CMV and HSV
- Rare: mycobacteria, protozoa, opportunistic neoplasms, drugs

After these are excluded...
- 40-55% Idiopathic esophageal ulceration (IEU)
Giant Esophageal Ulcers in AIDS

1. Idiopathic Esophageal Ulceration (IEU)
   - When known other causes of esophageal ulcers are excluded
   - Associated with HIV infection
   - Other names: esophageal aphthous ulcers, HIV esophagitis

   **Etiology uncertain:**
   - Attributed to high viremia, inflammatory cytokines, altered GI immunopathophysiology
   - HIV infection $\rightarrow$ apoptosis of esophageal mucosa

   **Symptoms:**
   - MC: odynophagia
   - dysphagia, chest pain substernal, burning sensation

   **EGD findings:**
   Ulcers = large, longitudinal, located in distal esophagus
   Surrounding Ulcer = erythema, edema
Diagnosis:
1. EGD with bx
2. r/o other infections via bx (histopathologic/immunologic exam):
   - CMV PCR, HSV PCR, Candida
3. Ulcers refractory to anti-CMV, anti-HSV therapy
4. r/o other causes of injury (meds, radiation)

Complications:
- esophageal stricture
- mucosal bridging
- sinus tract ulcers
- double-barreled esophagus appearance
- spontaneous esophageal rupture
Treatment:

1. **Prednisone**
   - 85% patients with ulcer healing (IEU decreased >50%)
   - concern further immunosuppression
   - relapse

2. **Thalidomide**
   MOA: interferes with TNF-alpha synthesis & mRNA production in HIV-1 monocytoid cell line → inhibits HIV
   - Symptomatic improvement
   - Endoscopic healing not 100%

3. **Misoprostol**
   MOA: suppresses TNF-alpha production, gastric antisecretory/cytoprotective
   * Inhibiting gastric secretion: topical application 3-6x more effective vs. systemic

4. **Antiretroviral therapy (alone)**
Treating IEU in HIV patients with Corticosteroids
AJG 1994

Comparison of Two Corticosteroid Regimens (non-randomized, non-blinded)
Identified pts from 1 hospital from 8/1990 – 12/1993 (Grady Memorial, GA)
- HIV
- EGD performed for odynophagia & showed >=1 esophageal ulcer (def: well-circumscribed mucosal break, 3mm depth): @ minimum 4 biopsies taken
  - Performed H&E stain, fungi, acid-fast
  - Performed in situ nuclei acid hybridization OR immunohistochemical stain for CMV, HSV (if granulation tissue OR atypical viral cytopathic effects seen)
- IEU = endoscopic & histopathologic ulcer WITHOUT identifiable viral cytopathic effect (routine, special stain) nor e/o pill-induced esophagitis or GERD

Prednisone Treatment groups:
1. 4 weeks: 40mg qDay, taper 10mg/week (n=12)
2. 2 weeks: 40mg qDay (n=24)

Things to Note:
- ketoconazole OR fluconazole administered during therapy
- NO antiacid or antiretroviral therapy initially
- Repeat EGD after therapy (when possible)
- Partial responders treated with increased dose (60 mg) +/- longer therapy (2-4 weeks)

Primary End Point:
*Complete response*: >90% reepithelialization of ulcer base, absence esophageal sx

Partial Response: >=50%reepithelialization of ulcer base, continued esophageal sx
- No significant difference between two groups
  - Mean ulcer number
  - Largest ulcer size
- Ulcers typically multiple, could be as large as 9cm
- f/u endoscopic evaluation
  - 4 week group: 8 of 12
  - 2 week group: 22 of 24

### Table 2

**Outcome of Prednisone Therapy**

<table>
<thead>
<tr>
<th></th>
<th>4-Wk</th>
<th>2-Wk</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Response [N(%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Complete</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Relapse [N(%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Partial</td>
<td>6</td>
<td>7</td>
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<tr>
<td>Complete</td>
<td>1–30</td>
<td>1–28</td>
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<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>0</td>
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</table>

* *p* = 0.10.
† Median.
Recommendation:
Prednisone effective in treating IEU in HIV
TOC is 4 weeks

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus esophagitis</td>
<td>2</td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>2</td>
</tr>
<tr>
<td>Cytomegalovirus retinitis</td>
<td>2</td>
</tr>
<tr>
<td><em>Candida</em> esophagitis</td>
<td>1</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Progression of Kaposi’s sarcoma</td>
<td>1</td>
</tr>
</tbody>
</table>

*One patient had *P. carinii* pneumonia and progression of Kaposi’s sarcoma.*
Treating IEU in HIV patients with Thalidomide
JIH 1999

Multicenter, double-blind, randomized, placebo-controlled trial
- HIV
- odynophagia OR dysphagia >=2 weeks
- Esophageal ulcer >=5mm (r/o infection, neoplasm, or other dx)
  - Neg HSV culture
  - If oral & esophageal ulcers, placed into another study for oral ulcers

Exclusion criteria: B peripheral neuropathy > grade I, corticosteroid use within 1 week before blood tests

Safety:
* Precautions for pregnancy
* Thalidomide adverse effects → dose could be changed/discontinued/withheld then resumed

Primary End Point:
* **Complete response** = Complete absence esophageal ulcers after 4 weeks (few pts in each arm had repeat EGD up to 7 weeks after)

**Partial Response** = decrease >=50% combined S.A. 3 largest ulcers compared to baseline + NO new ulcer formation
(S.A. = largest surface diam x largest perpendicular surface diam)

**Lack of Response** = decrease <50% in combined S.A. OR new ulcer
Trial: 24 pts (11 thalidomide, 13 placebo)
1. Assigned to 4 weeks of thalidomide (200 mg daily) vs. placebo
   - randomized, double-blinded

2. At the end of 4 weeks trial, if esophageal ulcers not healed
   ➔ offered open-label Thalidomide 200mg daily x 4 weeks
   ➔ After this period, if still not healed, offered Thalidomide 200mg bid x 4 weeks

Things to note:
- antiretroviral therapy held x 4 weeks prior to starting study
- CD4 ct < 200 cells/mm^3
- EGD at baseline, then 4 weeks later
- pts followed weekly
  1. evaluate side effects
  2. QOL questionnaire for pain/eating ability
- f/u labs: TNF-alpha RII serum, HIV RNA
Results:

**Complete Response @ 4 weeks**
Thalidomide: 8 of 11 (73%)
Placebo: 3 of 13 (23%)
OR 13.82, 95% CI 1.16-823.75, p = 0.033

**Complete OR Partial Response @ 4 weeks**
Thalidomide: 9 of 11 (82%)
Placebo: 4 of 13 (31%)
OR 11.06, 95% CI 1.16-195.09, p = 0.033

**Thalidomide group**
- 3 had neg immunohistochemical stain for CMV initially, but repeat ulcer bx +CMV
- 5 of 11 d/c or decreased dose due to adverse effect (but 4 had complete healing ulcers) vs. 1 in placebo
  * 1 d/c due to rash
  * Main adverse effects: peripheral sensory neuropathy, somnolence, rash
- QOL better compared to placebo (mild or no pain near end of 4 week treatment)
- median weight gain 1 kg vs. 1.8 kg weight loss in placebo
- Increase TNF-alpha RII & HIV RNA (not statistically significant)
Retrospective review (7 cases)
- Identified 7 pts with worsening odynophagia/dysphagia (taking standard antiretroviral tx & empiric antifungal tx)

Steps:
1. EGD with bx
   - r/o pathogens causing esophageal ulcers (bx, cytology, viral cx)
   - r/o H pylori with CloTest (not mentioned for pt #5)
2. Treatment
   Misoprostol 200 ug crushed/suspended 2% viscous lidocaine (15 mL)
   PO qAC & qHS x 4 weeks
   (8 weeks for pt #1)
3. Repeat EGD to evaluate healing
   - Variable when performed: 2, 3, 4 months (2 pts), 10 months
   (2 declined repeat EGD pts #3 and 6)
**Initial EGD finding: Esophageal Ulcers for Patient #:**

1. Two (8mm, 7mm) @ 35cm & 38 cm from incisors
2. One (2.5cm) @ 35 cm
3. Multiple @ 3cm above GEJ to proximal esophagus
4. Two (1cm, 1.5cm) @ 30cm & 38 cm (*CMV etiology of 1cm ulcer; also tx with ganciclovir*)
5. Two (3x2cm, 1.5x2cm) @ ?
6. Two (6mm, 8mm) @ 3cm above GEJ
7. One (4cm involving almost half of the esophageal circumference) @ ?
Things to Note

- Ulcers single or multiple
- All with odynophagia and weight loss
- All with low CD4 ct
- Rapid symptom improvement (within 3 days)
- Repeat EGD with complete healing esophageal ulcers (residual scar @ site)
- No documented side effects like diarrhea
Fig. 1. Case 1 (WDe). A) Esophageal ulcers at 35 and 38 cm from the incisors. B) Nearly complete healing of esophageal ulceration at 35 cm.

Fig. 2. Case 4 (CD). A) Esophageal ulceration at 38 cm from the incisors. B) Healed esophageal ulceration with minimal deformity at 38 cm from the incisors.
Treating IEU and Oropharyngeal Ulcers in HIV infection with Antiretroviral Therapy
Internal Medicine 2013

Case Report (timeline)
60 yo Japanese man, MSM p/w severe odynophagia
- CD4 cell ct 49/uL, HIV RNA 1x10^6 copies/mL
- neg CMV & HSV PCR serum

• **Empiric treatment with persistence of odynophagia & oral ulcers**
  1st. Fluconazole x 7 days (? esophageal candidiasis)
  2nd. Valaciclovir 1000 mg/day x 3 weeks (? HSV)

• **EGD #1**: large, discrete, well-circumscribed ulcers (pharynx, esophagus)
  Ulcer bx: edge & base

  3rd. Ganciclovir 5mg/kh q12 hours x 3 weeks (? CMV)

Pathology: lymphocytic infiltration WITHOUT intranuclear/intracytoplasmic inclusion bodies
- Neg CMV & HSV immunohistochemical stain
- Neg CVM & HSV PCR assays

• **EGD #2 (2 weeks after starting Ganciclovir)**: worsening of ulcers
  4th. Antiretrovirals (ritonavir boosted darunavir + abacavir/lamivudine)
Case Report cont’d

- 2 weeks after EGD #2
  Improvement
  1) Odynophagia
  2) CD4 ct 91/uL;
  HIV RNA 4x10^4 copies/mL

- EGD #3
  (day 22 of antiretroviral tx)
  Decrease in size/depth ulcers

Figure. Endoscopic findings of the pharynx and esophagus. The pharyngeal (a) and esophageal (b) ulcers before the administration of antiretroviral therapy. The endoscopic appearance of the pharynx (c) and esophagus (d) on day 22 of antiretroviral therapy. Black arrows: ulcers.
References:


Image: