

## CLINICAL VIGNETTE

# Refractory Heartburn – When the Purple Pill Doesn't Work

Lynn Connolly, MD, MSCR and Mary Farid, DO

### **Case Summary**

A 35-year old female with no significant past medical history presented to Gastroenterology with heartburn. She reported onset of intermittent heartburn symptoms as a teenager associated with upset stomach. The symptoms recurred briefly after college graduation but resolved with homeopathic treatments including aloe extract and licorice tablets.

Five years ago she started a new high stress job and was drinking 3 venti black coffees (60 ounces) or 8-10 espresso shots daily. She also started smoking 6 cigarettes daily. About six months into the new job, her heartburn symptoms restarted. At that time, she complained of acid in her throat, postprandial retrosternal burning, indigestion, bloating, gas and cramps. Spicy foods, dairy, coffee and alcohol were all triggers. She denied dysphagia, vomiting, weight loss, melena or anemia. OTC Famotidine (Pepcid AC) helped somewhat. Evaluation included normal basic blood work and unremarkable upper endoscopy. She was diagnosed with gastro-esophageal reflux disease (GERD) and started on treatment including diet and lifestyle modifications. She quit tobacco, cut back on caffeine to 1-2 cups daily and eventually the symptoms resolved. For two years she was relatively asymptomatic.

About one year ago her reflux symptoms returned with daily heartburn, indigestion, bloating and gas. She would wake up at night with an acid taste in the back of her mouth. She reported increased stress, working 100 hours a week as a casting director and only sleeping 4 hours a night. She resumed smoking and drinking coffee. When she had a six week break in her schedule and stopped smoking and drinking coffee, her symptoms completely resolved. Now that her work is stressful again, she is back to drinking 12 ounces of coffee and smoking 1-2 cigarettes daily. She has no dysphagia, odynophagia, nausea, vomiting, bleeding, constipation or diarrhea. Restarting OTC famotidine only helped about 30%. A friend recommended OTC daily omeprazole which led to only modest improvement compared to famotidine.

She was advised to cut back on tobacco, alcohol and caffeine and also minimize dairy given the bloating and cramping. Increasing the proton pump inhibitor (PPI) to 40mg twice daily made no difference compared to 20mg twice daily and, overall, she felt PPIs only help 30%.

Repeat upper endoscopy with biopsies was unremarkable. Laboratory tests were normal, including CBC, CMP, and celiac

antibody panel. Esophageal manometry was unremarkable. A Bravo pH study off of PPIs showed normal acid exposure and a positive symptom reflux association. She was diagnosed with reflux hypersensitivity and started on amitriptyline 10mg nightly. Treatment recommendations also included mindfulness stress reduction and a focus on sleep hygiene along with limiting caffeine, alcohol and tobacco. At 3-month follow up she was doing much better with almost no residual symptoms.

### **Discussion**

The differential diagnosis for refractory heartburn includes GERD, functional dyspepsia, functional chest pain, functional heartburn, reflux hypersensitivity, and overlap between GERD and either functional heartburn or reflux hypersensitivity.<sup>1</sup> A minimal response to acid suppressing medications raises the question of esophageal hypersensitivity, including reflux hypersensitivity or functional heartburn. Upper endoscopy is performed to rule out erosive esophagitis, eosinophilic esophagitis (EoE) and other structural causes of heartburn. Esophageal manometry is performed to rule out major esophageal disorders. For example, the prevalence of heartburn has been reported to be as high as 35% in achalasia.

Reflux hypersensitivity identifies patients with heartburn or chest pain who lack evidence of reflux on upper endoscopy or abnormal acid exposure on pH monitoring yet show triggering of symptoms by physiologic reflux events (Table 1).<sup>2</sup> The Rome IV diagnostic criteria for reflux hypersensitivity includes retrosternal symptoms including heartburn and chest pain with a frequency of at least twice a week for the past 3 months with symptom onset at least 6 months before the diagnosis (Table 2). Major esophageal motility disorders and eosinophilic esophagitis must be ruled out with a motility study and upper endoscopy. It is important to note that a response to antisecretory therapy does not exclude the diagnosis of reflux hypersensitivity.<sup>3</sup>

Mechanisms of esophageal symptoms in reflux hypersensitivity include esophageal hypersensitivity, abnormal central processing of esophageal signals, hypervigilance, emotionally related factors and psychological comorbidity. The impact of psychosocial influences must be evaluated including depression, anxiety, PTSD, excessive worry about symptoms, major stressors, and early adverse life events.

Treatment of reflux hypersensitivity includes modulators of visceral sensation and behavioral interventions. Pain modulators for the treatment of functional esophageal disorders include TCAs, SSRIs, and SNRIs (Table 3).<sup>4</sup> Behavioral interventions include psychological therapies such as hypnotherapy, cogni-

tive behavioral therapy, mindfulness-based stress reduction, meditation, and psychotherapy. Acupuncture, relaxation techniques and biofeedback have also been used to reduce symptoms in reflux hypersensitivity.

**TABLE 1. Evaluation of Heartburn with pH monitoring off or on Proton Pump Inhibitors (PPIs)**

	<b>pH monitoring Off PPI:</b>		<b>pH study ON PPI</b>	
	Acid Exposure Normal or Abnormal?	Symptom reflux association?	Acid Exposure Normal or Abnormal?	Symptom reflux association?
Functional Heartburn	Normal	Negative	n/a	n/a
Reflux Hypersensitivity	Normal	Positive	n/a	n/a
NERD	Abnormal	Positive or Negative	n/a	n/a
GERD	Abnormal	n/a	Abnormal	n/a
GERD + Functional Heartburn Overlap	Abnormal	n/a	Normal	Negative
GERD + Reflux Hypersensitivity Overlap	Abnormal	n/a	Normal	Positive

**TABLE 2. Rome IV Diagnostic Criteria for Reflux Hypersensitivity**

*Criteria must be fulfilled for the past 3 months with symptom onset at least 6 months before diagnosis with a frequency of at least twice a week.*

Must include all of the following:

1. Retrosternal symptoms including heartburn and chest pain
2. Normal EGD and absence of evidence that EoE is the cause for symptoms
  - a) Absence of major esophageal motor disorders (achalasia/EGJ outflow obstruction, DES, jackhammer esophagus, absent peristalsis)
  - b) Evidence of triggering of symptoms by reflux events despite normal acid exposure on pH or pH-impedance monitoring

**TABLE 3. Pain Modulators for the Treatment of Functional Esophageal Disorders**

Tricyclic Antidepressants (TCAs)

- Desipramine 10-40mg daily
- Amitriptyline 10-20mg daily

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Sertraline 25-100 mg/day
- Citalopram 20mg/day

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine 75 mg/day

Other

- Gabapentin 300mg TID
- Trazadone 100-150 mg/day

## REFERENCES

1. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional Esophageal Disorders. *Gastroenterology*. 2016 May;150(6):1368-1379.
2. Roman S, Gyawali CP, Savarino E, Yadlapati R, Zerbib F, Wu J, Vela M, Tutuian R, Tatum R, Sifrim D, Keller J, Fox M, Pandolfino JE, Bredenoord AJ; GERD consensus group. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: Update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil*. 2017 Oct;29(10):1-15. doi: 10.1111/nmo.13067. Epub 2017 Mar 31. Review. PubMed PMID: 28370768.
3. Yamasaki T, Fass R. Reflux Hypersensitivity: A New Functional Esophageal Disorder. *J Neurogastroenterol Motil*. 2017 Oct 30;23(4):495-503. doi: 10.5056/jnm17097. Review. PubMed PMID: 28992673; PubMed Central PMCID: PMC5628981.
4. Nguyen TM, Eslick GD. Systematic review: the treatment of noncardiac chest pain with antidepressants. *Aliment Pharmacol Ther*. 2012 Mar;35(5):493-500. doi: 10.1111/j.1365-2036.2011.04978.x. Epub 2012 Jan 13. Review. PubMed PMID: 22239853.