

CLINICAL MANAGEMENT

Refractory Heartburn

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Clinical Case

A 33-year-old woman presents to her primary care physician with a chief complaint of heartburn for the past 12 months. She describes this as a severe burning discomfort beneath the breastbone occurring throughout the day. The patient has no history of dysphagia, vomiting, weight loss, or gastrointestinal bleeding. She reports regurgitation once a month, unchanged in the recent past. Reasoning that her heartburn is likely caused by gastroesophageal reflux disease (GERD), her physician prescribes omeprazole 20 mg daily. Two weeks later the patient phones her physician to report that her heartburn is unchanged. He advises her to increase the dosage of omeprazole to 20 mg twice daily and schedules a return office visit 4 weeks later. At that office visit, the patient reports no more than a 10%–15% improvement in her heartburn. The patient is referred to a gastroenterologist for advice on evaluation and management.

Background

In attempting to develop an all-encompassing definition of GERD, the Genval Working Group arrived at the following, “. . . all individuals who are exposed to the risk of physical complications from gastroesophageal reflux or who experience clinically significant impairment of health-related well being (quality of life) due to reflux-related symptoms. . .”.¹ Given that the patient described above presents mainly with a symptom burden, we are faced with the task of determining whether or not she is experiencing “impaired quality of life due to reflux-related symptoms.” Thus, from a diagnostic viewpoint, to attribute her refractory heartburn to GERD, the symptom burden must (1) be to a degree that impairs quality of life, and (2) those symptoms must be reflux-related. Put another way, symptoms must be of sufficient severity to constitute a disease (the “D” in GERD) and the symptoms must be attributable to GER. From a management viewpoint, the objective is to reduce the patient’s symptom burden, irrespective of causality. However, at this point we have only a failed management strategy and no diagnosis.

Has the Patient’s Heartburn Impaired Her Quality of Life?

Essentially the entire literature on the impact of GERD symptomatology on quality of life has focused on the frequency and severity of heartburn with the assumption that heartburn is attributable to GER. Illustrative of this, the Genval Working Group accepted (with some reservation) that “Health-related well being is impaired in proportion to the frequency of heartburn.”¹ Thus, the symptom-based definition of GERD ultimately becomes a quantitative issue. In attempting to define the quantitative limits of that definition, the Genval Working Group also accepted that when heartburn occurs on 2 or more days a week it impairs an individual’s quality of life enough to be considered a disease. However, whereas well-designed cohort or case-controlled studies were cited in support of the first opinion, the second opinion was based only on case reports or flawed clinical trials. The Working Group’s hesitancy in accepting a rigid quantitative definition is understandable because an average is just that, an average. In some cases, individuals are greatly troubled by a lesser symptom burden and in other cases, they trivialize a far greater one. Thus, from a clinical vantage point, it is the patient who decides whether their condition is best described as GER or GERD. Furthermore, there is a multitude of factors, including emotional factors, social circumstances, and support structures, that dynamically modify whether or not the “D” is appropriate. Given that this patient has sought and pursued medical care for her condition, there is little question about the appropriateness of the “D”; the bigger question is whether or not the “D” is attributable to GER.

Abbreviations used in this paper: GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

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Is the Patient's Heartburn Attributable to GER?

The most characteristic and frequently encountered GERD symptom is heartburn. Furthermore, given the high background prevalence of GERD in the United States, there is a very high predictive value of GERD as the diagnosis when heartburn is the dominant or exclusive symptom.² However, one potential diagnostic pitfall in this association is that patients often misuse the term "heartburn" making it incumbent upon the clinician to clarify the intended meaning. The salient characteristics of heartburn are as follows. Heartburn is characterized by a discomfort or burning sensation behind the sternum that arises from the epigastrium and may radiate toward the neck. Heartburn is an intermittent symptom, most commonly experienced within 60 minutes of eating, during exercise, and while lying recumbent. The discomfort is relieved with drinking water or antacid but can occur frequently and interfere with normal activities. Contemplating this description, one is immediately concerned as to whether or not it applies to the patient under discussion. Certainly, she has not reported the typical exacerbating and alleviating factors and she has, after all, failed the "PPI test" as it has come to be known.

The managing physician's decision to empirically render therapy with omeprazole, and to then increase that therapy to twice-daily omeprazole amounted to his performing a therapeutic trial. A proton pump inhibitor (PPI) is an ideal agent for a therapeutic trial because of impressive efficacy in treating all acid-related disorders (including GERD) and a superb safety profile. Given that the key management objective is symptom relief, this approach is appealing. What better way of detecting individuals with symptoms that will respond to a medication than to administer the medication and gauge the response? However, knowing that someone responds to a given PPI regimen does not establish a GERD etiology any more than their not responding to this regimen rules it out. In the case of the responder, it is the symptom-reflux association and/or endoscopic findings that establish the diagnosis. In the case of the nonresponder, it could be an instance in which this therapy is inadequate, or it could be that the presumptive diagnosis is incorrect. In the case under discussion, the patient estimates a 10%–15% response. For all intents and purposes, this is no response. We are left then with finding explanations for this unimpressive response. Potential explanations include: inadequate therapy, nonreflux causes of esophagitis, esophageal hyperalgesia, nonacid reflux, or functional heartburn. How should we proceed?

Potential Management Strategies

Many gastroenterologists would argue that endoscopy before this point in management would have been helpful. The rationale would be that early endoscopy might reveal peptic esophagitis that will no longer be evident after 4–6 weeks of PPI treatment or, somewhat less commonly, endoscopy would detect the occasional case of infectious or pill esophagitis that would invoke an alternate management strategy. Some would even argue that pH monitoring should have been performed if the endoscopy was negative or equivocal. However, the general consensus amongst gastroenterologists in 2003 is that uncomplicated heartburn does not warrant investigation and that empiric therapy is an appropriate clinical strategy. Thus, the predicament we find ourselves in with this patient is not uncommon; a highly symptomatic individual who has not responded to a therapy that usually works very well. Where do we go from here? In broad terms, there are 3 management options: (1) increase the potency of GERD therapy or offer an alternative GERD therapy (medical, surgical, intraluminal); (2) pursue diagnostic testing with endoscopy, pH monitoring, etc; or (3) empirically treat the patient with a low-dose tricyclic antidepressant on the presumption that she is experiencing functional heartburn.

Recommended Management Strategy

Given the management options delineated above, this author would argue for some degree of evaluation before any further therapeutic intervention. Mind you, at this point there is minimal relevant literature on which to base a management strategy because this is the type of patient that one usually endeavors to exclude rather than include in clinical trials and the literature is reflective of that. Thus, it really does come down to clinical experience, level "E" evidence from the lofty perspective of evidence-based medicine. Be that as it may, my rationale for not pursuing options 1 or 3 is as follows. Escalating GERD therapy at this point is unlikely to work. Twice daily PPI therapy is a very effective treatment for heartburn and, even when not completely effective, the patient's subjective assessment of efficacy generally far exceeds 10%–15%. Usually, by the time therapy has escalated to this point and still proven ineffective, there is enough uncertainty and unease about the diagnosis on the part of the patient, the referring physician, and myself that all parties favor a diagnostic evaluation. With respect to empiric therapy with a tricyclic for presumptive functional heartburn, this intervention would be premature. Functional heartburn is, by defini-

tion, a diagnosis of exclusion and, so far, we have not excluded anything. Thus, an upper endoscopy is arranged. Because I would have a strong suspicion that the endoscopy will be normal, I would simultaneously arrange to do ambulatory esophageal pH monitoring with the caveat that it would be cancelled should the endoscopy yield definitive findings.

One question that emerges with respect to the ambulatory pH monitoring study is whether it should be done with the patient on or off omeprazole. This is almost always a difficult question because there is a rationale for doing the test either way. However, you want objective evidence of quantitatively abnormal acid exposure or significant reflux-heartburn association, and on the other hand you want to see whether or not the omeprazole is effective. In fact, in some particularly difficult cases, the test ends up being done twice to accommodate both needs. However, in the setting of this clinical vignette we as yet have no objective evidence of GERD or reflux-related symptoms. Furthermore, although testing for PPI refractory reflux is conceptually appealing, no data exist to evaluate the results of such patients remaining on PPI therapy. Furthermore, there are no published reports of esophageal pH data on patients who had symptoms that responded to PPI therapy obtained while they were taking their PPI regimen. This, coupled with the fact that the patient has had no significant response to omeprazole and that the omeprazole would likely compromise the sensitivity of the pH monitoring study, argue strongly for doing the pH monitoring study with the patient having refrained from taking omeprazole for 5–7 days.

Another critical aspect of the pH monitoring study is that every effort be made to ascertain whether or not the patient's heartburn episodes are correlated with reflux events. This is important because, in all likelihood, the pH monitoring findings for our patient are going to be quantitatively normal and it is the presence or absence of a reflux-symptom correlation that will determine the next therapeutic intervention. Within the realm of symptom-reflux association schemes, 3 have been described: (1) the symptom index, (2) the symptom sensitivity index, and (3) the symptom-association probability. An important distinction between them is that whereas with both the symptom index and the symptom sensitivity index, a "positive" score is arbitrarily (as opposed to statistically) defined, the symptom-association probability, statistically compares the temporal relationship between pH data and reported symptoms, in this case heartburn.³ The statistical approach utilizes contingency table analysis and Fisher exact test to analyze the

four potential associations of heartburn and pH data: reflux and heartburn; reflux and no heartburn; no reflux and heartburn; and no reflux and no heartburn. The result is a probability that heartburn and reflux are associated and a P value of less than 0.05 is a positive association. The symptom-association probability is then reported as $(1.0 - P \times 100\%)$ with 95% taken as a positive result. This feature clearly makes the symptom-association probability the best scheme available, but it is important to recognize that all of these schemes of symptom-reflux correlation were devised from retrospective analyses of pH data and that none has been prospectively validated against an independent parameter of diagnostic accuracy.

Evolution of the Case

An endoscopy is performed and the esophageal mucosa appears normal. The squamocolumnar junction is 39 cm from the incisors and sharply demarcated. No mucosal erosions and no hiatus hernia are noted. The stomach and duodenum appear normal. At the end of the endoscopic procedure, a Bravo (Medtronic Inc., Minneapolis, MN) pH-monitoring capsule is affixed 33 cm from the incisors.⁴ The patient had discontinued taking omeprazole 7 days before the endoscopy.

Two days later the patient returns with the pH monitoring apparatus. She had tolerated the test well and was able to eat normally and conduct her usual activities for the 2 days of the study. Evaluation of the tracing reveals successful capture of a 48-hour pH recording. Esophageal acid exposure on days 1 and 2 was 1.2% and 2.7% respectively; essentially all of this occurred during the day during post-cibal periods. During the entire period of the recording the patient indicated that she experienced heartburn on 27 occasions, all during the day. Three heartburn events occurred within 2 minutes of periods that the esophageal pH was less than 4; the remainder did not. The symptom-association probability was not significant (36%).

Subsequent Management

The above data were interpreted to indicate that the patient does not have GERD and her syndrome was categorized as "functional heartburn." The observed association between her reflux and heartburn on the pH study was no better than chance, and she had no endoscopic findings suggestive of GERD or other pathology. She is prescribed imipramine 25 mg daily before bed and reassured that her symptoms are not manifestations of heart disease, cancer, or other life-threatening conditions. Six weeks later she reports an 80% improvement in her heartburn.

Functional Heartburn

To quote from the Rome II definitions regarding functional GI disorders, "functional esophageal disorders represent chronic symptoms that typify esophageal disease yet have no identifiable structural or metabolic basis."⁵ Functional heartburn is subsequently defined as "episodic burning in the absence of pathological reflux, pathology-based motility disorders, or structural explanations. The term can still be applied to those patients whose symptoms are associated with acid reflux events during ambulatory pH monitoring, provided that the duration of esophageal acid exposure is normal."⁵ Obviously, there is something of an inconsistency in these definitions with respect to the final point. From the author's perspective, if the patient's symptoms are attributable to reflux, then it is not functional heartburn regardless of the quantitative aspects of the pH monitoring study. Such an individual, with a quantitatively normal pH study but strong symptom-reflux association, might be labeled acid-sensitive esophagus or even visceral hyperalgesia but either way the entity still belongs within the universe of GERD. However, the individual with functional heartburn has symptoms suggestive of reflux without physiologic evidence of reflux and without any physiological explanation for symptoms. The important clinical distinction between the two is that the patient with functional heartburn is unlikely to respond to any treatment for GERD whereas the acid-sensitive esophagus will, albeit less perfectly. The patient under discussion in this vignette best fits the description of functional heartburn and one could cogently argue that, despite often being classified as having endoscopy-negative reflux disease, such patients do not really fit within the diagnosis of GERD at all.

Data on functional heartburn are essentially nonexistent but psychosocial factors are often invoked. Early life experiences and influences may modify a patient's perception and interpretation of esophageal symptoms. A higher frequency of physical and sexual abuse has been reported among patients with functional gastrointestinal disorders in general.⁶ Many patients note that heartburn symptoms are increased and/or more frequent during times of psychological and emotional stress. However, studies have demonstrated no significant quantitative difference in acid reflux during stressful events.^{6,7} It has been proposed that these patients may have a psychological tendency to report more symptoms than the general population and that anxiety in these individuals may lead to cortical amplification of low to moderate intensity afferent signals from esophageal receptors.⁶ Finally, it is worth noting that various psychiatric disorders such as

depression, obsessive-compulsive behavior, somatization, and anxiety disorders are more prevalent in these patients.

There is minimal treatment literature with respect to functional heartburn per se but from the author's experience the population exhibits considerable overlap with the nonreflux esophageal chest pain population. Because it is apparent that psychological factors play a role in esophageal chest pain, antidepressant medications have been used in the treatment of patients with esophageal hyperalgesia, including chest pain patients. These agents have been found to reduce chest pain in symptomatic patients with esophageal contraction abnormalities.⁸ However, other studies have been somewhat conflicting. Imipramine was found to significantly raise the threshold for pain but not sensation to intraesophageal balloon distention in normal males.⁹ In another study, amitriptyline had no effect on the perception of esophageal distention despite a significant effect on the perception of somatic electrical stimulation.¹⁰ However, these negative results were obtained in healthy controls and no data currently exist on the modification of esophageal sensitivity in disease states.

Conclusions

The first conclusion to draw from this clinical vignette is that refractory heartburn is very rarely related to refractory esophagitis. PPIs are so effective in treating all severities of esophagitis as to designate the rare refractory case meritorious of a case report. However, such is not the case with heartburn relief, be it in the setting of endoscopy-positive or endoscopy-negative disease. The endoscopy-negative group is further complicated by being heterogeneous, comprised of at least 3 broad subgroups of patients as discussed later.

The first subgroup to consider is the simplest; patients with similar pathophysiology to esophagitis, but whose disease is undetected by endoscopy. Included in this group are patients whose endoscopy was negative because of the intermittent nature of the mucosal lesions of esophagitis, because of prior or ongoing treatment that has healed their esophagitis, or because of the inherent limited sensitivity of endoscopy in detecting subtle esophagitis. In the case of healed or intermittently occurring esophagitis, quantitative esophageal pH monitoring can be used to detect GERD. In the case of subtle lesions, studies utilizing quantitative histopathologic methods¹² or measurement of mucosal potential difference¹³ have revealed abnormalities of the esophageal epithelium in patients who did not meet esophagitis criteria according to the Los Angeles grading scale.

The second 2 groups of endoscopy-negative patients are similar in that they both have a symptom complex consistent with a GER etiology and both lack any demonstrable abnormality of the esophageal epithelium. They differ in that in one group a reflux etiology can be established and in the other it cannot. To put it another way, they both have the "D" but in one case it is attributable to GER and in the other it is not. However, making this distinction in clinical practice can be difficult because of our imperfect tools for establishing whether or not symptoms are attributable to reflux; be it acid reflux, nonacid reflux, or gas reflux.¹⁴

Finally, endoscopy-negative patients categorized as having a "D" on the basis of heartburn severity but in whom heartburn is not attributable to GER (exemplified by the subject of this vignette) do not have GERD at all. Often, they have underlying psychosocial factors at the root of their symptomatology and from a clinical vantage point they are more likely to respond to low-dose tricyclic antidepressants than to antisecretory medications. Nonetheless, knowing that patients fit into this category of "functional heartburn" is useful in that it allows the clinician to provide them with strong reassurance regarding the benign nature of their affliction and it protects them from therapeutic misadventures targeting a disease that they do not have, e.g., GERD.

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