



A Unique Case of Non-cardiac Chest Pain Caused by Mepolizumab: Case Report and Review of the Literature

Introduction

Non-cardiac chest pain is defined as chest pain that is identical to ischemic chest pain but with a reasonable workup excluding cardiac causes.¹ Evaluation with upper endoscopy, esophageal manometry, and pH monitoring is typically performed to rule out gastrointestinal etiologies. Studies have shown that around half of patients who experience non-cardiac chest pain have abnormal pH testing.²⁻⁵ In this case report, we describe the first case of non-cardiac chest pain caused by mepolizumab, a medication used in the treatment of asthma.

Case Report

A 66-year-old man presented to his primary care provider multiple times for chest pain between March 2016 and April 2018. His chest pain was described as left-sided to substernal, dull, and non-radiating. These symptoms were intermittent, lasting no more than 5 minutes, and occurred approximately once per week. After the initial visit he was referred to a cardiologist with an extensive negative evaluation. He was then referred to a gastroenterologist. He underwent esophagogastroduodenoscopy which showed a small hiatal hernia. Esophageal manometry testing revealed normal motility with a hiatal hernia. Additionally, 24-hour impedance pH study was performed that was negative for both acid and non-acid reflux. He continued to have chest pain on pantoprazole 40 mg twice daily and ranitidine 150 mg nightly, therefore nortriptyline 10 mg nightly was supplemented for possible functional component. He remained on this regimen for 1 year without clinical success, therefore nortriptyline was increased to 20 mg nightly for a few months, once again without symptom alleviation. Extensive review of his medication was performed given the unusual nature of the chest pain. It ap-

peared that mepolizumab was initiated for treatment of his asthma about 1 month prior to the onset of his chest pain, therefore, it was decided to discontinue mepolizumab and switch to benralizumab. In subsequent visits, the patient achieved near complete resolution of his symptoms.

Discussion

We describe an interesting case of medication-induced non-cardiac chest pain. Mepolizumab is a humanized monoclonal antibody against IL-5 and is primarily used as an adjunctive treatment for eosinophilic asthma.⁶ IL-5 is a cytokine responsible for the growth, recruitment, activation, and proliferation of eosinophils, which are key mediators in reactive airway inflammation and disease, particularly in asthma.^{7,8} The most common adverse events reported with mepolizumab administration are headache, injection-site reactions, back pain, and fatigue.^{7,8} To our knowledge, this is the first case of non-cardiac chest pain associated with mepolizumab. Interestingly, in a previous clinical trial investigating the use of mepolizumab in exacerbations of refractory eosinophilic asthma, there was 1 patient who developed chest pain in the treatment group, whereas no patients in the placebo group reported chest pain.⁹

Our patient experienced approximately 2 years of recurrent, non-cardiac chest pain despite an extensive evaluation and treatment with acid suppression. Upon discontinuing mepolizumab and switching to another IL-5 antagonist, benralizumab, he experienced near complete resolution in chest pain after 3 months. Benralizumab has a similar mechanism of action to mepolizumab in functioning as an IL-5 antagonist, however it also increases the affinity of natural killer cells for eosinophils, inducing eosinophil apoptosis.⁸ In addition, benralizumab binds to IL-5 with a dissociation constant of 16 pM, compared with 100 pM of mepolizumab, which may be one of the causes for the different adverse event profiles.¹⁰

While the pathogenesis of mepolizumab-induced chest pain

is unknown, it is critical to keep all medications in mind, especially biologic agents, as a potential cause of non-cardiac chest pain. The authors suggest that if a patient presents with refractory non-cardiac chest pain, a thorough medication history and reconciliation should be pursued to look for unlikely etiologies and perhaps further our understanding of non-cardiac chest pain.

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1. Fass R, Achem SR. Noncardiac chest pain: epidemiology, natural course and pathogenesis. *J Neurogastroenterol Motil* 2011;17:110-123.
2. Stahl WG, Beton RR, Johnson CS, Brown CL, Waring JP. Diagnosis and treatment of patients with gastroesophageal reflux and noncardiac chest pain. *South Med J* 1994;87:739-742.
3. Beedassy A, Katz PO, Gruber A, Peghini PL, Castell DO. Prior sensitization of esophageal mucosa by acid reflux predisposes to reflux-induced chest pain. *J Clin Gastroenterol* 2000;31:121-124.
4. DeMeester T, O'Sullivan GC, Bermudez G, Midell AI, Cimochofski GE, O'Drobinnak J. Esophageal function in patients with angina-type chest pain and normal coronary angiograms. *Ann Surg* 1982;196:488-498.
5. Pandak WM, Arezo S, Everett S, et al. Short course of omeprazole: a better first diagnostic approach to noncardiac chest pain than endoscopy, manometry, or 24-hour esophageal pH monitoring. *J Clin Gastroenterol* 2002;35:307-314.
6. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-1207.
7. Fala L. Nucala (mepolizumab): first IL-5 antagonist monoclonal antibody FDA approved for maintenance treatment of patients with severe asthma. *Am Health Drug Benefits* 2016;9:106-110.
8. Pelaia C, Calabrese C, Vatrella A, et al. Benralizumab: from the basic mechanism of action to the potential use in the biological therapy of severe eosinophilic asthma. *Biomed Res Int* 2018;2018:4839230.
9. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-984.
10. AstraZeneca Canada Inc. (Feb. 22, 2018). Fasenna: Benralizumab injection. Retrieved from <https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/fasenna-product%20monograph-en.pdf> (accessed December 27, 2019).

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