Journal of Gastrointestinal & Digestive System

Brodie et al., J Gastrointest Dig Syst 2017, 7:5
DOI: 10.4172/2161-069X.1000530

Case Report OMICS International

# A Favorable Response of Dysplastic Barrett's Refractory to Ablation Therapy Only after Initiation of an Alginate Solution as Add-on Therapy

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**Received date:** September 20, 2017; **Accepted date:** September 27, 2017; **Published date:** October 05, 2017



**Abstract**

Alginates have been shown not only to be beneficial in their relief of symptomatic post-prandial gastroesophageal reflux, but there is also evidence that they may inhibit reflux, including bile acids and pepsin, and in turn attenuate and even prevent the activation and up-regulation of molecules associated with the development of metaplasia and cancer of the esophagus. Here we present the case of a patient with Barrett's esophagus with high-grade dysplasia (HGD) which was initially unresponsive to endoscopic radiofrequency ablation therapy and cryotherapy for high-grade dysplasia. Following initiation of therapy with an alginate solution in addition to twice daily proton pump inhibitor (PPI) therapy, the patient showed a favorable response and eventual complete eradication of his dysplastic Barrett's. The patient's course is suggestive that the alginate solution, through reflux inhibition, prevented persistent esophageal cell changes which occur secondary to gastric and bile acid exposure, thus allowing development of neosquamous epithelium. This case is intriguing with regard to the role of alginates in creating a favorable environment for esophageal healing when treating Barrett's esophagus with high-grade dysplasia.

**Keywords:** Gastroesophageal reflux; Endoscopy; Proton pump inhibitor; Hernia

## Case Study

### HPI

A.H. is a 46 year old male with history of hiatal hernia and gastroesophageal reflux disease (GERD) who presented to our tertiary referral center for management of long segment dysplastic Barrett's esophagus with high-grade dysplasia (HGD) which had been refractory to treatment with radiofrequency ablation (RFA). The patient had undergone five rounds of RFA at an outside medical center with less than 50% improvement of his dysplastic Barrett's at the time of the fifth endoscopy. His last endoscopy prior to transfer had revealed residual dysplastic Barrett's in the lower esophagus, and biopsies showed persistent HGD. On presentation to our center, the patient reported that his acid reflux was not well-controlled despite twice daily PPI. He complained of heartburn, night time regurgitation, and non-productive cough. Review of systems was otherwise negative for chest pain, shortness of breath, dysphagia, odynophagia, weight loss, abdominal pain, nausea, vomiting, or other complaints.

**Past medical history:** Small (2 cm) Hiatal hernia.

**Past surgical history:** None.

**Social history:** Negative for tobacco, alcohol, or illicit drug use; lives overseas, returns to the states roughly 4 times per year.

**Family history:** Non-contributory.

**Medications:** Esomeprazole 40 mg BID, Sucralfate 1 g QID.

**Treatment course:** After a long discussion with the therapeutic endoscopy team, options other than RFA such as endoscopic mucosal resection and cryotherapy were discussed. Given the distribution, anatomy and flat nature of his Barrett's esophagus, cryotherapy was started and he began receiving treatments every two months starting in July 2014. After the first three treatments, there was minimal endoscopic evidence of improvement in the surface area of Barrett's epithelium with less than 50% improvement, so ablation exposure times were increased from 20 to 30 seconds.

This still resulted in only mild improvement in appearance of his Barrett's after a total of six cryotherapy treatment sessions. Because of the lack of response, manometry and pH/impedance testing were completed to assess for dysmotility and ongoing acid exposure in the esophagus.

Manometry showed ineffective esophageal motility (IEM), while his pH/impedance study revealed that while acid control was good in the stomach and no abnormal acid exposure was occurring in the esophagus, there was significant persistent non-acid reflux. Due to these findings along with less than 50% improvement from initial appearance of the patient's Barrett's and persistent reflux symptoms despite twice daily PPI therapy and night-time H2 blocker therapy, the patient was tried on Bethanechol therapy in an attempt to improve his esophageal motility and possibly decrease his GERD symptoms.

He had minimal response and multiple side effects, so this was discontinued. He was then started on a twice daily alginate solution (Gaviscon Advance, EU version, 15 mL packets to be taken following meals and at night) instead of H2 blocker therapy for better attempted control of his reflux. After initiation of this therapy at 8 months, and following his 7$^{th}$ treatment of cryotherapy, endoscopy revealed roughly 75% improvement in his Barrett's dysplasia.

Following two additional treatments, EGD revealed full resolution of the patient's dysplastic Barrett's. Over one and a half years later, he continues to have complete resolution of BE while being maintained on twice daily PPI and twice daily alginate therapy.

## Discussion

**Background:** Alginates are polysaccharides found most widely in the cell walls of seaweed (brown algae). They have been implicated in a variety of uses, including symptomatic relief of gastroesophageal reflux disease. They have been marketed over the past 40 years most notably as the non-prescription medication Gaviscon, which is advertised as a dual action antacid, containing both alginate and typical antacid (i.e. calcium carbonate) [1].

**Mechanism:** The mechanism of action of alginates involves the formation of a protective barrier on the surface of the gastric contents. The alginate itself precipitates into a gel in the presence of gastric acid. Concurrently, the bicarbonate in alginate-based solutions forms carbon dioxide in the presence of gastric acid, which converts the gel into foam which floats to the surface of the gastric contents [1]. Hence, alginate solutions form "rafts" which provide a physical barrier to acid reflux, as well as a pH-neutral substitute which refluxes into the esophagus preferentially over gastric acid [2]. Furthermore, alginates are thought to target the acid pocket, an unbuffered pool of acid that floats on top of ingested food and causes postprandial acid reflux.

In patients with hiatal hernias, scintigraphy demonstrated alginate/antacid formulations to better target the acid pocket, keep the acid pocket more often below the diaphragm, and pH impedance demonstrated fewer reflux events when compared to antacid alone [3]. Furthermore, MRI has demonstrated radiolabeled alginate to preferentially settle on the surface of gastric contents, while radiolabeled antacid was demonstrated to settle to the distal stomach [4]. Finally, supporting the "raft" model, Castell et al. demonstrated with pH monitoring that the superiority of alginates over antacids in post-prandial reflux exists primarily in the upright (as contrasted with supine) position [5].

**Efficacy in relief of GERD symptoms:** In addition to having been shown to be superior to placebo in relieving symptoms of GERD, alginates have also demonstrated non-inferiority to PPI in this regard, as well as superiority to placebo as add-on therapy for patients already on PPI [6-8]. Furthermore, dual action antacids (antacid with alginate) have been shown to be superior to antacids alone in reducing post-prandial esophageal acid exposure in GERD patients [9].

**Bile Acid control and implications for cancerous and pre-cancerous changes:** Alginates target the gastric acid pocket and provide a barrier between gastric contents and the esophagus. Since gastric contents consist of more than just gastric acid, the use of alginates has implications beyond symptomatic relief. In addition to hydrochloric acid, refluxate can include pepsin, bile acids, and pancreatic enzymes. There is good reason to believe that controlling reflux of these contents into the esophagus has health benefits as well. Specifically, the ability of alginates to form a formidable barrier between damaging and even cancer-causing molecules and the esophagus suggests deterrence of esophageal damage and oncogenesis.

Pepsin and gastric acid, and not acid alone, have been shown to lead to cell damage equivalent to esophagitis [10-13]. Bile acids have been shown to be damaging to esophageal epithelial cells by affecting membrane permeability, cell proliferation and differentiation, increasing free radicals, inducing DNA damage and up-regulating oncogenes [11,14-20]. More specifically, both gastric acid and bile acids have been shown to activate NF-kappa B, a major molecule that is up-regulated in and intrinsic to cancer development. This has been demonstrated in esophageal epithelial cells in both a dose and time-dependent manner [21,22].

There have been numerous other studies which have shown bile acids to be integral to the development of esophageal metaplasia, as well as conversion of Barrett's esophagus to esophageal adenocarcinoma [23,24]. Interestingly, Gaviscon has been shown to retard diffusion of bile acids and remove bile acids from simulated reflux events *in vitro* [25]. In the same study, Gaviscon also removed pepsin from the reflux event in a dose-dependent manner. A separate study exposed *in vitro* esophageal cell lines to deoxycholic (bile) acid in the presence and absence of alginates, and measured levels of oncogene up-regulation. It was shown that the alginate prevented induction and upstream effects of multiple oncogenes that are associated with GERD changes that lead to Barrett's esophagus and adenocarcinoma [26].

## Conclusion

Alginates have been shown not only to be beneficial in their relief of symptomatic post-prandial gastroesophageal reflux, but there is also evidence that they inhibit the reflux of bile acids and pepsin into the esophagus, and in turn attenuate and even prevent the activation and up-regulation of molecules associated with the development of metaplasia and cancer of the esophagus. Here we present the case of a patient with Barrett's esophagus that was initially unresponsive to endoscopic radiofrequency ablation therapy and cryotherapy for high-grade dysplasia.

Following addition of an alginate solution, the patient showed a favorable response and eventual complete eradication of his dysplastic Barrett's. The patient's course is suggestive that the alginate solution, through additional means of reflux inhibition, prevented persistent esophageal epithelial cell changes which occur secondary to gastric and bile acid exposure, thus allowing development of neosquamous epithelium. The case of A.H. is intriguing with regard to the role of alginates in creating a favorable environment for esophageal healing post cryotherapy. Further studies are warranted to compare the response of treatment for dysplastic Barrett's with or without the addition of alginate solutions.

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