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The long road to diagnosis, from gastroesophageal reflux disease, through Barrett's esophagus, to visceral hypersensitivity: a case report

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ABSTRACT:

Background: Visceral hypersensitivity syndrome is a condition involving excessive perception of mechanical stimuli in the intestines. In patients suffering from this disorder, physiological bowel function causes pain and discomfort.

Case summary: The patient presented is a 26-year-old man with severe gastrointestinal symptoms that were difficult to manage, such as heartburn, pressure in the esophageal region, a sensation of a gullet in the throat, food retention, and frequent belching. The man had been experiencing these symptoms intermittently for four years, during which time he had been treated without success. By way of exclusion, a diagnosis of visceral hypersensitivity was made, and a low dose of amitriptyline was administered. Psychological therapy was also recommended. This treatment brought significant improvement and resulted in the resolution of his complaints.

Conclusions: Visceral hypersensitivity is strongly associated with psychosocial factors, which should be taken into account when treating patients with gastrointestinal disorders. Low doses of amitriptyline may be an effective treatment option.

Keywords: visceral hypersensitivity; case report; gastroesophageal reflux disease; irritable bowel syndrome; therapy; small intestine bacterial overgrowth

CASE PRESENTATION:

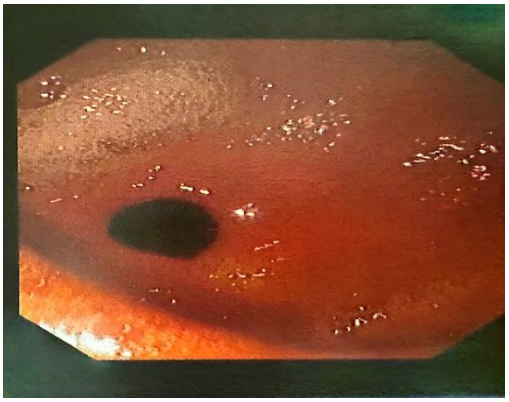
In October 2023, a 26-year-old patient presented to the gastroenterology clinic complaining of gastrointestinal symptoms. His main problem was heartburn, which occurred from the morning after the first sip of water and lasted all day, regardless of the type and amount of food consumed. He also reported diffuse pain in the left hypogastric region, which periodically passed during the day, pressure in the esophageal region, a feeling of a gullet in the throat, food retention, and frequent belching.

The man was a medical student and had been treated for 9 years for Hashimoto's disease, for which he was taking the drug Euthyrox 25 mg once a day. There was no history of food or drug allergies. The patient's body weight was stable; his BMI was 23.5. The patient was active in handball, training 3 times a week. The man reported that the onset of his ailment was 4 years ago, and he had already undergone several different therapies with short or no improvement.

The first symptoms appeared at the end of 2018. At that time, the patient presented with stabbing abdominal pain in the left subcostal region of medium intensity, as well as a feeling of food retention in the esophagus. The doctor suspected gastroesophageal reflux disease (GERD), so prescribed Prokit 50mg x 3 times a day, Dexilant 30 mg once a day, and an easy-to-digest diet. After the therapy, the patient experienced improvement. The patient was also referred for a gastroscopy. Gastroscopy showed an incompetence of gastric cardia, suspected esophageal metaplasia, gastritis of the antrum of the stomach, and biliary reflux. Whereas, pathomorphological examination revealed esophageal sections containing glandular utricle corresponding to a gullet-type mucosa with chronic active inflammatory infiltration, with intestinal metaplasia, and without dysplasia. Based on a positive urease test, the patient was treated for Helicobacter Pylori with a combination of the drugs metronidazole 500mg x2 daily, amoxicillin 1g x2 daily, and Dexilant 30 mg once daily for 10 days. Symptoms gradually decreased, and the patient attempted to discontinue all medication, which was successful. In

2019, the symptoms recurred. He felt a pain in the left subcostal region, which changed to diffuse pain, lasted most of the day, and increased shortly after meals. Sometimes, there were also hiccups lasting 1-3 days, pain in the esophageal region, a feeling of food retention, frequent belching, flatulence, and irregular and frequent bowel movements. The doctor prescribed Debretin 100mg x 3 daily and recommended a Mediterranean diet and physical activity. Despite the patient's compliance, this had no significant effect.

At the beginning of 2021, the treatment was no longer completely effective, and the patient additionally began to complain of increased production of gases and bloating. Small intestinal bacterial overgrowth (SIBO) was suspected, and treatment with Xifaxan 200mg x3 daily was implemented. Improvement was noticeable for several months. Subsequently, diffuse left lower abdominal pain increased, and persistent heartburn reappeared, accompanying the patient almost after every meal. A fecal test showed the presence of H. Pylori. The doctor reintroduced combination pharmacotherapy: metronidazole 500mg x2 daily, amoxicillin 1g x2 daily, and Dexilant 30 mg once daily for 10 days. The symptoms resolved for 3 months. In 2022, the gastrologist recommended symptomatic use of Esoxx One and Gaviscon one hour after meals and before going to bed. He also prescribed a colonoscopy and a repeat gastroscopy, taking sections from the esophagus to test for eosinophilic esophagitis and from the stomach due to intestinal metaplasia that had been detected in the previous examination. Results revealed gastritis, biliary reflux, and suspected Barret's esophagus. On histopathological examination, the specimen showed an active inflammatory infiltrate, glandular epithelial hyperplasia, and areas of intestinal metaplasia without features of dysplasia. The clinical picture on examination was not consistent with eosinophilic esophagitis. Colonoscopy showed no abnormalities.



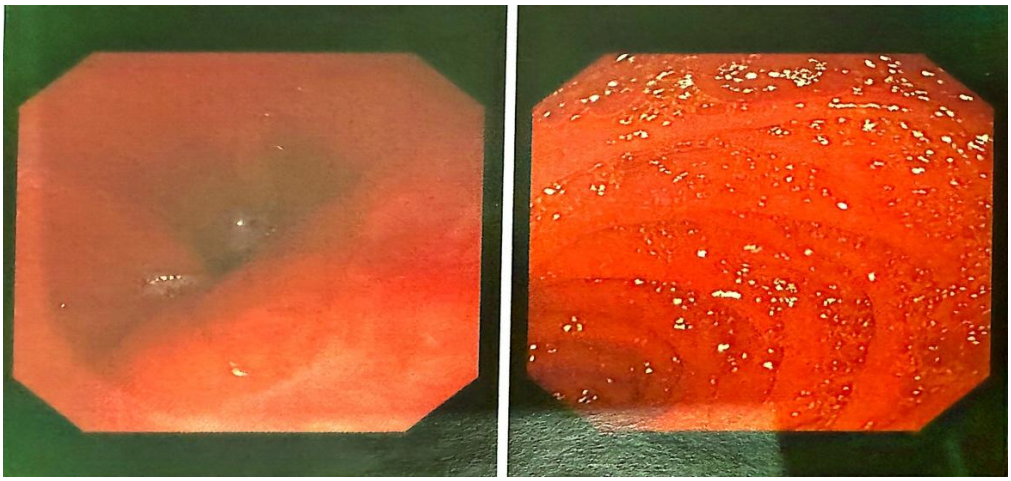


Figure 1. Images taken during the 2022 esophageal endoscopy examination.

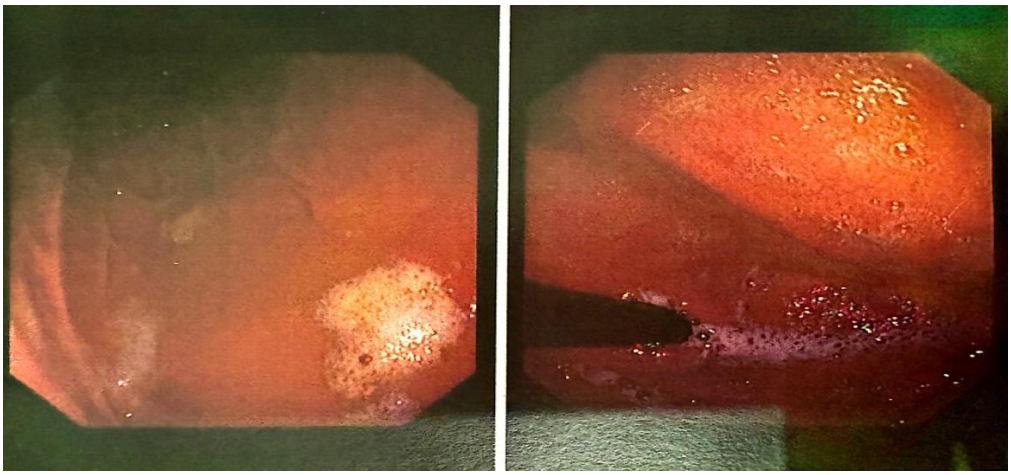


Figure 2. Images taken during the 2022 esophageal endoscopy examination.

In the meantime, the man started psychotherapy and also used the services of a dietician. He was advised to take sodium butyrate supplements, Enterol, and symptomatically mastic, as well as hydrogen-methane tests and pH metry. The hydrogen-methane test detected SIBO, so Xifaxan 400mg 3x daily therapy was reintroduced. PH metry showed no abnormalities. The dietician recommended the introduction of a low FODMAP diet, which resulted in an alleviation of the discomfort, but not a complete resolution.

Due to a long history, non-specific symptoms throughout the gastrointestinal tract, inconclusive endoscopic findings and multiple drug therapies with no results, the diagnosis was directed towards visceral hypersensitivity. Treatment with Amitriptyline 10 mg once a day for the first week, then 25 mg once daily for 3 months was prescribed. Psychotherapy and discontinuation of all other previously prescribed medication was recommended. The nature of

the problem and his complaints were carefully explained to the patient, emphasizing the possible important role of psychological factors.

After three months, the man confirmed at his follow-up examination that most of his manifestations had disappeared, and he felt significantly better. After one year, patient reports further significant improvement and resolution of complaints. He is currently not taking any medication except Euthyrox. He continues psychotherapy and tries to implement anti-stress techniques into his daily life. During psychological therapy, he was diagnosed with anxiety, which he is also working intensively on.

DISCUSSION:

Visceral hypersensitivity (VH) syndrome is characterized by an abnormal sensation of physiological stimuli in the intestines, which manifests as pain and discomfort. In non-pathological conditions, functions such as bloating and gastrointestinal contractions do not cause pain or discomfort. Individuals with VH have an increased perception of mechanical stimuli. (1), (2) Visceral hypersensitivity consists of hyperalgesia and allodynia. Hyperalgesia is a pain response to factors that normally cause pain. Allodynia, on the other hand, occurs when normal stimuli cause an increase in nociception in the patient. (3) This disorder is often accompanied by diseases that fall into the biopsychosocial category, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), or functional dyspepsia (FD). (4) It has been shown that the basis of VH is a reduced threshold for sensing gastrointestinal stimuli. (1), (2), (5) The prevalence of VH in patients with IBS varies between 33 and 90% in various studies (6),(7),(8), peaking in patients with IBS-D who show increased intestinal permeability. (9),(10). The occurrence of VH in patients with IBS is associated with significantly higher complications than in those without hypersensitivity. The localization of the disorder is not only the rectum and sigmoid colon, as originally indicated by studies. It has been confirmed that VH can occur in all parts of the gastrointestinal tract, including the small intestine, stomach, and also the esophagus (5),(7),(11),(12). An example of such a case is the presented patient, whose symptoms affected the entire gastrointestinal tract.

The pathogenesis of VH is not fully understood. It is known to be a multifactorial process, the origin of which may lie at both central nervous system (CNS) and peripheral nervous system levels. Factors such as microbial infections, gut microbiota, psychological

factors, inflammatory factors, immunological factors, brain-gut communication, diet, and genes are also potential causes. (13), (14), (15), (16), (17). Many people with IBS, which is strongly associated with VH, have altered pain perception in the gut through disruption of the gastrointestinal, immune system, and neuronal pathways. (19) Bacteria and intestinal pathogens can directly affect visceral afferents and disrupt the intestinal barrier. (20), (21) Nociceptive transmission and sensation changes may also be associated with intestinal neuroendocrine factors. (22)

The important role of psychological and social factors in the development of VH should be emphasized. Studies among patients with IBS, which is strongly associated with VH (3), indicate that episodes of depression occur in 20-30% of them and anxiety in 15-45%, which is significantly more common than in healthy patients. It has been confirmed that psychosocial factors can exacerbate visceral pain symptoms, as well as IBS, by affecting brain-gut interactions, bowel function, and pain perception. (18) This is also perfectly illustrated by the case of our patient, in whom psychological factors were responsible for his persistent complaints. Symptomatic treatment proved ineffective, and improvement was only brought about by work on stress management, psychological therapy aimed at reducing anxiety, and low-dose antidepressants.

Pharmacotherapy for patients with VH symptoms classically includes symptomatic treatment of diarrhea, constipation, abdominal pain, flatulence, and heartburn. Consequently, remedies such as loperamide or mesalazine for diarrhea (23) or polyethylene glycol and lactulose for constipation are used to alleviate this discomfort. (24) Antispasmodics are also used for abdominal pain, and carminatives for flatulence. (25) This was similar for the presented patient, who was initially treated for GERD and also symptomatically for his complaints. Drugs related to the psychosocial aspects of VH and IBS are also used. These include tricyclic antidepressants such as imipramine, clomipramine, and nortriptyline and selective serotonin reuptake inhibitors such as citalopram and fluoxetine. (26), (27). Low doses of amitriptyline (AMT), which were also introduced in the presented case, have proven efficacy in reducing abdominal pain in patients with IBS and functional dyspepsia (FD). (28), (29), (30), (31) Their effect in this regard is not related to the antidepressant effect, as the doses used are lower than the effective ones for the antidepressant drug. Their impact is observed in patients who do not suffer from depression and takes place before the antidepressant action. (32) Research suggests that the beneficial impact of AMT, administered at low doses, is based on its influence on brain activation in the anterior cingulate cortex and the left posterior parietal complex. These are the areas responsible for experiencing pain during psychological stress. The drugs have also been

shown to reduce gastric sensitivity and increase plasma levels of ghrelin and neuropeptide Y. (33) There are also studies indicating that several natural compounds such as curcumin, dicentrine, ginseng saponins, berberine, and tetrahydropalmatine may have potential in reducing visceral pain. (3)

CONCLUSSIONS:

The case presented here perfectly illustrates the complexity of problems in patients suffering from gastrointestinal disorders. Diagnosis in such situations can be difficult, inconsistent, and often achieved by exclusion.

It is essential to pay attention to psychosocial factors that can significantly impact the development of visceral hypersensitivity. We can note the first clues during the interview, guiding us in the correct diagnostic direction. However, it is essential to conduct appropriate investigations to check for other possible causes. Sometimes, this process can take several years, as the patient presented. In the case described, the man seems to have fallen into a vicious circle. The longer his complaints persisted, the more treatments failed, and the more worrying the diagnoses became, the greater his stress about his health was. That is why it is so important to refer the patient for psychological or psychiatric help and to make him aware of the significance of psychosocial factors in the development of the problem. This case also demonstrates that low-dose amitriptyline therapy can be very effective in patients with this problem.

ABBREVIATIONS

VH Visceral hypersensitivity
GERD Gastroesophageal reflux disease
SIBO Small intestinal bacterial overgrowth
IBS Irritable bowel syndrome
IBD Inflammatory bowel disease
FD Functional dyspepsia

DISCLOSURE

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