Chapter

Extraesophageal Manifestations and Symptoms of Esophageal Diseases

Ljiljana Širić, Marinela Rosso and Aleksandar Včev

Abstract

Esophageal diseases are diagnosed by gastroenterological processing indicated due to typical gastrointestinal symptoms, but typical gastrointestinal symptoms are not the only possible manifestation of esophageal disease. There are also external symptoms such as chronic cough, laryngitis, pharyngitis, oropharyngeal dysphagia, odynophagia, laryngopharyngeal reflux, dysphonia, sinusitis, ear pain, and changes in laryngopharyngeal mucosa (erythema, edema, ventricular obliteration, cricoid hyperplasia and pseudosulcus). Extraesophageal symptoms are common in esophagitis and GERD, and studies show increasing prevalence of LPR in patients with GERD, as well as an association of reflux disease with cough and dysphonia symptoms. The aim of the chapter is to describe these extraesophageal symptoms of esophageal disease and how to recognize and treat them, in order to facilitate gastroenterologists' diagnostic processing of patients with these symptoms, improve their treatment and assessment of the therapy effectiveness, prevent the development of stronger symptoms, and encourage multidisciplinary cooperation and exchange of knowledge, scientific and clinical work.

Keywords: chronic cough, chronic laryngitis, dysphonia, esophagitis, laryngopharyngeal reflux

1. Introduction

Due to anatomical location and function, esophageal motility disorders, inflammatory diseases, gastroesophageal reflux (GER), esophageal rings and webs, tumors and other esophageal conditions and diseases can cause many extraesophageal symptoms, which are increasingly recognised and diagnosed by otolaryngologists, pulmonologists, cardiologists, and, of course, gastroenterologists. Certain pathophysiological conditions that are not localized in the esophagus may be the first symptoms of esophageal disease or signs associated with the onset of esophageal disease. One of the etiological factors is the pathophysiological mechanism of the increase in intra-abdominal pressure that occurs during weight gain and in pregnancy. Another etiological factor is the pathophysiological mechanism of relaxation of the lower esophageal sphincter that may occur due to coronary heart disease drug therapy rich in nitrates. A similar thing happens during antirheumatic therapy in rheumatoid arthritis and some degenerative

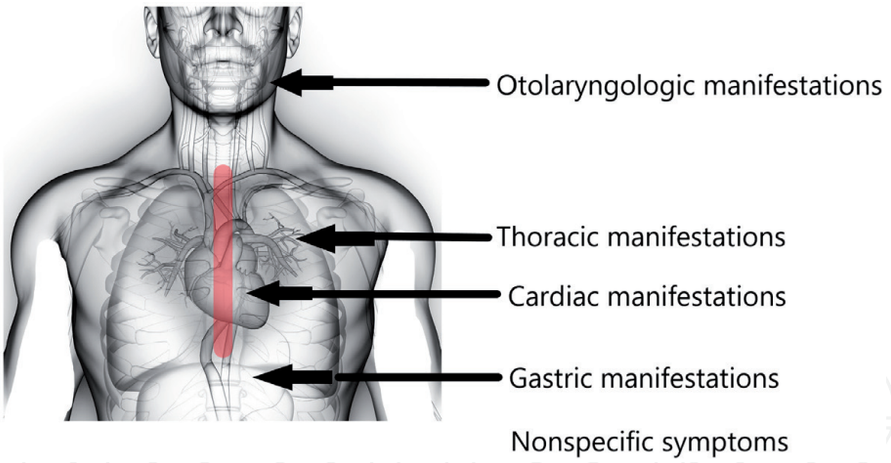

Figure 1.
Extraesophageal manifestation of esophageal diseases.

diseases of the locomotor system. Other conditions that may be associated with gastroesophageal reflux and esophageal diseases include diabetes mellitus, which results in prolonged gastric stagnation and consequent prolonged gastric emptying, and duodenal ulcer, duodenal stenosis, or malignant gastric disease in which delayed gastric emptying is present. So far, it is a well-known fact that the appropriate speed of food passage through the gastrointestinal tract, which is conditioned by a series of autoregulatory processes, is important. An optimal rate of passage is required - small enough to complete food digestion and absorption of substances and large enough to supply the body with the necessary nutrients in a timely manner [1]. The most common atypical symptoms of esophageal disease, primarily esophagitis and gastroesophageal reflux disease (GERD), will be listed here. For better visibility and easier understanding, the classification of atypical extraesophageal symptoms was performed according to the criterion of anatomical localization (**Figure 1**):

- otolaryngological manifestations
- thoracic manifestations
- cardiac manifestations

And last but not least, the biopsychosocial dimensions of esophageal diseases and extraesophageal symptoms are being recognized, too.

2. Otolaryngologic manifestations

2.1 Chronic laryngitis and laryngopharyngeal reflux (LPR)

Patients with reflux laryngitis often have characteristic anamnestic data and records in the history of the disease. Common symptoms of laryngitis include chronic or intermittent recurrent cough, chronic sore throat, hoarseness, clearing of the throat, dry mouth, feeling of a 'lump' and tickling in the throat, nocturnal dyspnea, laryngospasm and dyspepsia. Inspection of the laryngeal mucosa may reveal erythema and edema of the mucosa covering the arytenoid cartilage, the posterior part of the larynx, and often the posterior part of the true vocal cords.

Two theories explain the pathogenesis of reflux laryngitis:

1. theory of direct injury of the laryngeal mucosa and surrounding tissue by acid and pepsin;

2. reflex theory [2].

Due to direct injury to the laryngeal and pharyngeal mucosa, mucociliary transport is damaged and secretions accumulate in the throat, which causes additional irritation of the mucosa and contributes to the symptoms of postnasal drip, throat clearing and foreign body sensation in the throat. As the larynx lacks the protective external cleansing and salivary mechanisms that neutralize acid, gastric reflux remains undiluted for a long time, resulting in tissue injury. The action of pepsin leads to the depletion of the carbonic anhydrase isoenzyme III, and it catalyzes the reversible hydration of carbon dioxide resulting in the production of bicarbonate ions. The formation of bicarbonate ions directly neutralizes the acidic stomach contents and inactivates pepsin, so the ions actually protect the tissue from acid refluxate [3, 4]. On the other hand, depletion of carbonic anhydrase isoenzyme III reduces the neutralization of acidic gastric contents and allows its prolonged activity. According to the reflex theory, laryngopharyngeal reflux occurs due to esophageal reflux that stimulates vagal-mediated reflexes, resulting in a subjective need to 'clear' the throat and a chronic cough that leads to injury to the laryngeal mucosa. Laryngopharyngeal reflux is a clinical entity that represents the return of gastric contents to the space of the larynx and hypopharynx, which causes the contact of acid with the tissues of the upper aerodigestive tract [5]. In the physiological state, the upper and lower esophageal sphincters act together and prevent reflux of gastric contents into the esophagus and upper aerodigestive tract. Howewer, the pathophysiology of LPR is typically attributed to a defect or dysfunction of the upper esophageal sphincter. The esophagus features a number of protective mechanisms which prevent injury of the mucosa, which the laryngopharyngeal mucosa do not possess, and are more susceptible to damage from acid reflux. Laryngeal epithelium is up to 100 times more susceptible to pepsin damage than esophageal tissue [6]. Regurgitation of the contents may cause primary burning and/or sore throat, cough, need for excessive throat cleansing, and secondarily may cause symptoms such as dysphonia, productive expectoration and globus hystericus (feeling of a 'lump' in the throat). Signs of laryngopharyngeal reflux are visible in the form of laryngeal irritations, hyperemic mucosa of the vocal cords and arytenoids, thinned vocal cords, posterior pharyngeal wall abnormalities, erythema, edema, and discontinuity of mucosal continuity. Of these symptoms, laryngeal irritations and abnormalities of the posterior pharyngeal wall have a statistically significant prevalence in patients with reflux. It should be noted that these symptoms, in addition to esophagitis and gastroesophageal reflux disease, are also present in persons exposed to allergens and irritants and in postnasal drip syndrome. Most authors interpret laryngopharyngeal reflux as atypical gastroesophageal reflux, although some authors disagree with this interpretation given the different pathophysiology and symptomatology of these refluxes [7]. It is important to emphasize that the etiology of reflux in laryngopharyngeal and gastroesophageal reflux is not the same, just as the form and circumstances of occurrence are not quite the same. For example, laryngopharyngeal reflux occurs more often during the day in an upright position, while gastroesophageal reflux occurs in a horizontal position and at night, or during sleep. Different body composition of patients with laryngopharyngeal and gastroesophageal reflux [8] was also observed, and published studies show an association between increased body mass index (identified as obesity) and gastroesophageal

reflux disease [9] and a statistically significant higher incidence of gastroesophageal reflux disease in patients with registered obesity. In contrast, increased body mass index is not statistically significant in patients suffering from laryngopharyngeal reflux [10, 11]. Reflux associated with laryngeal symptoms is verified by laryngoscopy and 24-hour pH monitoring. Patients with laryngopharyngeal reflux without alarming symptoms are treated empirically with proton pump inhibitors for one to two months. If this type of therapy is effective, according to individual needs, the therapy is extended to six months with the aim of complete healing of the laryngeal and pharyngeal mucosa.

2.2 Dysphonia

Chronic gastroesophageal reflux is an etiological factor that contributes to the manifestation of laryngeal symptoms, primarily hoarseness. In addition to hoarseness, laryngopharyngeal reflux and laryngitis may occur. Koufman et al. found that 78% of dysphonic patients have gastroesophageal reflux disease [12]. According to Vashana, acid reflux is especially common in singers. The author explains this statement in several facts: muscle activity due to a vocal technique that works against the lower esophageal sphincter; inadequate feeding and sleep dynamics; emotional components and exposure to stressors typical of this profession [13].

2.3 Chronic rhinosinusitis (CRS)

More recent studies has reported significant association between gastroesophageal reflux and chronic rhinosinusitis, but the nature of the association is still unknown. Gastroesophageal reflux disease can cause several upper airway symptoms and change the physiology of nasopharyngeal mucosa, while upper airway diseases might also exacerbate GERD symptoms [14]. This associaton can be explained by three physiological mechanisms: the direct effect of acid or acidic vapor in the nasal mucosa, a dysfunction of the autonomous nervous system and the presence of Helicobacter pylori. It is known that the direct contact of the acid with the nasopharyngeal mucosa results in mucosal edema, with reduction of the mucociliary clearance and obstruction of the sinusal ostium. The acid reflux is an uncommon event in the nasopharynx and occurs in only 5% of GERD patients. Autonomic dysfunction, in this case the increase of the vagal tonus, may partly account the hyper-reactivity of the airways to acid. The Heliobacter pylori has been identified in the esophagus, palatine and tonsils, saliva and teeth, and is not known how its presence can result in some abnormalities of this tissues. Retrospective studies describe an improvement of 69 to 89% of the nasosinusal symptoms after GER treatment. Despite this knowlege, it is still not possible to state that the gastroesophageal reflux is one of the leading risk factors to chronic rhinosinuitis, but it must be researched as an unchaining factor when there is no other evident etiology. Howewer, GER symptoms are very prevalent in patients with chronic rhinosinusitis [15].

2.4 Chronic otitis media (COM)

Chronic otitis media may lead to tympanic membrane perforation as a consequence of unresolved and resistant middle ear infection, blockage of the Eustachian tube, insufficiency of ciliary clearance, or an injury to the ear persisting more than 3 months. Various microorganisms are considered as etiologic agents in COM. Other predisposing factors may also play role in persistence of the disease. Many recent studies have shown a potential association between gastroesophageal reflux

and otitis media chronica [16]. Gastroesophageal reflux can be an inflammatory cofactor and can result in upper respiratory tract disorders, including COM in pediatric and adult age group. Otitis media with effusion is the most common cause of hearing loss in children. The pathogenesis is multifactorial: infections, impaired immunologic status, allergic history, anatomical problems, familial predisposition and enviromental factors have role in pathogenesis. The angle and length of the Eustachian tube are more horizontal and shorter in infants than in adults, and may allow reflux of gastric contens from the nasopharynx into the middle ear. It can cause to lay the groundwork for mucociliary clearance dysfunction and bacterial infections. Some studies found pepsin concentrations in samples from middle ear effusions of up to 1000-fold greater in children who undergone myringotomy. It was suggested that the GER may be related to glue ear in children. The therapy of COM is mainly surgical. Higher level of damage in the middle ear of patients having GERD requires appropriate treatment which may positively affect outcomes for COM surgery [17].

2.5 Oral mucosal changes

More recent studies have pointed out that extraesophageal symptoms of GERD are acidic lesions of the oral mucosa. These lesions are caused by direct acid and pepsin exposure, or acidic vapor contact in the oral cavity. GERD was reported to be associated with microscopic alterations in the palatal mucosa, such as epithelial atrophy, deepening of epithelial crests in connective tissue and a higher prevalence of fibroblasts [18]. Mucosal changes are quite common and not pathognomonic and specific of patients with gastroesophageal or esophagopharyngeal reflux, but erythema of the soft palate and uvula, epithelial atrophy, xerostomia and glositis are quite common in GERD patients. Some authors pointed out the presence of aphtoid lesions, hoarseness, chronic periodontitis, dry oral mucosa with a keratotic appearance of the gingival tissues and the presence of burning mouth. In addition, persons with GERD may complain of a sour or acidic taste, impaired taste (dysgeusia), an oral burning sensation and water brash (flooding of the mouth with saliva in response to an esophageal reflux stimulus) [19]. Adequate mucin-rich salivary secretions coat all of the internal anatomical surfaces and are essential for the protection of the oropharyngeal and esophageal mucosa and the teeth from chemical, thermal, mechanical and microbial damage. Saliva also facilitates efficient swallowing and speech. Some studies have found a significant association between gastroesophageal reflux and hyposalivation. On the other hand, proton pump inhibitors can cause hyposalivation. Hyposalivation may result in xerostomia, impaired mastication and swallowing, painful mouth, cracked lips and angular cheilitis [20].

2.6 Hypersalivation

The quantity of salivation and the quality of saliva can be an indicator of a certain disease of the oropharynx and esophagus or it can be an indicator of the complication of such conditions. Saliva is produced by the parotid, submandibular and sublingual glands and the small salivary glands. Sialoreia usually occurs in neurological diseases, such as Parkinson's and Wilson's disease, Angelman's syndrome, infections, heavy metal poisoning, and can also occur in the secretory phase of the menstrual cycle or as idiopathic paroxysmal sialoreia. Increased salivation can be caused by systemic consumption of drugs with a cholinergic effect (clozapine, risperidone, nitrazepam, lithium and bethanekol), and it also occurs as a subtle manifestation of gastroesophageal reflux disease in the form of 'water

brash'. However, hypersalivation, although uncomfortable and disruptive, does not necessarily have to be negative since saliva plays an important role in protecting the esophageal mucosa. There are studies on the importance of ingested saliva that neutralizes the pH of gastric acid regurgitated into the esophagus [21] and on the buffering of gastric acid that enters the esophagus by reflux [22]. The acid that accumulates in the upper part of the esophagus reflexively initiates the formation of saliva [23], which is not the case when the acid accumulates in the lower part of the esophagus [24].

2.7 Dental erosion

Chronic regurgitation of gastric acids in patients with gastroesophageal reflux and related condition - laryngopharyngeal reflux may cause dental erosion which can, in combination with attrition or bruxism, lead to extensive loss of coronal tooth tissue. Dental erosion is typically a slowly-progressing and ireversibile phenomenon defined as the loss of tooth substance by chemical processes (acid exposure) not involving bacteria [25]. The literature shows a strong correlation between GERD and dental erosion, with a median prevalence of 24% in a large range of age groups. The degree of erosion due to GERD is related to the duration of the disease, frequency of reflux, the pH and type of acid, and the quality and quantity of saliva. Demineralisation and the loss of calcium and phosphate ions from the mineral surface of the teeth result in visible defects, and cause significant reduction in microhardness which makes the softened surface more prone to mechanical damage [26]. It is recognized that refluxed acid attacks the palatal surfaces of the upper incisor teeth first, later, if the condition continues, erosion of the occlusal surfaces of the posterior teeth in both arches and the labial or buccal surfaces [27].

2.8 Halitosis

Halitosis is an unpleasant odor from the oral cavity and is a condition that affects a large number of people [28]. The prevalence of halitosis is 8–46% [29]. The pathophysiological mechanism of halitosis is still not completely clear and is mainly attributed to oral pathology due to microbial activity in the interdental space, between the teeth and periodontium, and on the dorsal side of the tongue. Published data suggest that halitosis may correlate with chronic sinusitis, upper and lower respiratory tract diseases, various systemic diseases, gastroenterological diseases, and consumption of certain drugs in patients without oral pathology. It has been stated that mouth breathing, too, can be the cause of halitosis [30]. Although halitosis has previously been considered a rare consequence of gastrointestinal disorders [31], recent literal data have shown that it is common in gastrointestinal pathology and is significantly more common in patients with gastroesophageal reflux disease than in healthy individuals [32]. Furthermore, the symptom is often present in patients with verified infection with Helicobacter pylori, a bacterium that is among the major pathogenic factors of inflammatory and ulcerative changes on the gastric mucosa [33–36]. In addition, a high correlation has been demonstrated between halitosis and gastroesophageal reflux disease and peptic ulcer disease [37], and some authors have linked halitosis to volatile sulfur compounds [30, 38, 39] and to the chemical compounds cadaverine, some types of indoles [30]. Cadaverine (1,5-pentanediamine) is a toxic diamine formed by tissue putrefaction. Indole (benzopyrrole) is a heterocyclic compound formed by the breakdown of the amino acid tryptophan in the digestive tract, however, it is also used in the production of certain drugs, fragrances and essential oils [40]. An organic compound from the indole family associated with halitosis is skatol (3-methylindole), which occurs naturally

in faeces, it is also present in flowers and essential oils (orange and jasmine) in low concentrations, and is used as a fixative in many perfumes [41]. A 2006 study by Lee et al. reported that Helicobacter pylori produces hydrogen sulfide and methyl mercaptan that contribute to halitosis [42], and the bacterium itself is one of the main factors in the manifestation of gastrointestinal diseases.

3. Thoracic manifestations

Thoracic manifestations can occur secondary to the wide range of esophageal disorders: inflammatory process, infections, trauma and perforation, congenital malformations, esophageal motility disorders and benign and malignant neoplasms. Complications associated with these diseases and disorders can involve the mediastinum, tracheobronchial tree, and lungs. Lower respiratory system and esophagus share a common embryological derivation and are anatomically related. Pulmonary complications can be associated with high morbidity and mortality. Such complications can be categorized as:

1. mediastinal complications (due to trauma, perforation, foreign bodies, caustic injury, or malignancy);

2. tracheobronchial complications (congenital or acquired tracheoesophageal fistulas);

3. pleural complications (esophagopleural fistulas);

4. lung complications (due to GERD, infectious and inflammatory process) [43].

Gastroesophageal reflux disease has been linked to a variety of respiratory diseases either as a direct cause, or as a risk factor to the inability to control or worsening of the disease. It can cause various pulmonary manifestations and nonspecific complaints: chronic cough and fewer, recurrent pneumonia, noncardiac chest pain, sputum production and dyspnoea, bronchospasm. Epidemiological studies in patients with reflux esophagitis have shown an increased risk for chronic bronchitis, chronic obstructive pulmonary disease, pneumonia, and idiopathic pulmonary fibrosis. Chronic cough and bronchial asthma are more common respiratory manifestations of GERD. Pathological GERD has been described in 30% to 80% of patients with asthma. Micro-aspiration of gastric contents and/or vagal irritation from gastro esophageal reflux may constitute airway irritants and thus represent a potential pathogenic mechanism for acute illness or acute exacerbations of chronic pulmonary diseases. Exacerbations of chronic obstructive pulmonary disease is twice as high in patients with GERD as in those without GERD symptoms. GERD can produce lung disease by two mechanisms: by reflex neural mechanisms occuring during reflux events limited to the lower part of esophagus, and direct from gastric contents refluxed into the pharynx producing upper airway damage and lung disease. While gastroesophageal reflux may increase airways resistance and cause inflammation by releasing pro-inflammatory mediators, esophagopharyngeal reflux creates the potential to aspiration and its consequences which varies depending of the duration, volume and nature of the aspirate [44]. Chronic cough is considered to be a cough that is continuously present for eight weeks and longer. Among the etiological factors, the three most common causes of chronic cough can be singled out: postnasal drip syndrome, asthma and gastroesophageal reflux. In 75% of cases, patients with chronic cough do not have the typical symptoms of

esophagitis or gastroesophageal reflux disease, yet the result of 25% of patients with symptoms of both types speaks in favor of the association of chronic cough and esophageal disease [45]. Namely, the determination of correlation is primarily based on the strength and direction of the correlation, and not only on the frequency and percentage of results.

4. Cardiac manifestations

Coronary heart disease and gastroesophageal reflux disease can interact and produce chest pain. Some recent studies have shown that exposure of the esophageal mucosa to acid can compromise myocardial perfusion and cause chest pain by inducing coronary spasm or cardiac dysrythmia [46–48]. On the other hand, myocardial ischemia can cause esophageal dysmotility or relaxation of the lower esophageal sphincter and exacerbate GERD [49]. GERD can worsen sleep disturbances, and sleep apnea increases the risk of a cardiovascular diseases [50]. These two diseases have a number of common risk factors and comorbidities, such as diabetes, hypertension, hyperlipidemia, smoking and alcoholism, gender and age [51, 52]. Proton pump inhibitors, as a treatment option in GERD therapy can also affect cardiovascular physiology. One of the big population-based study shows that PPI usage can reduce the cardioprotective effects of certain therapies, and it can also reduce the contractility of myocardial tissue and raise the risk of atherosclerosis by increasing the serum levels of homocysteine by impairing the absorption of vitamin B12. This study indicates that GERD is associated with an increased risk of developing coronary heart disease, and PPI therapy that lasts longer than one year might increase the risk of CHD [53].

5. Conclusion

Esophageal symptoms are common and often overlap between different esophageal disorders, making a diagnosis based solely on patient history, symptoms, and physical presentation challenging. Esophageal motility disorders often manifest with chest pain and dysphagia. Other symptoms are heartburn, regurgitation, weight loss and malnutrition. Chest pain is localized behind the sternum, and does not spread to the shoulders and arms, which distinguishes it from cardiac pain. Gastroesophageal reflux (GER) symptoms have been reported in up to 20% of the adult population, which makes GER one of the common gastrointestinal disorders with a chronic or recurrent nature. Patients often complain of heartburn and acid regurgitation. The presence of this symptoms at least once a week for the last 3 months are considered essential in diagnosis of a clinical disorder called gastroesophageal reflux disease (GERD) [54]. Gastroesophageal reflux is often associated with symptoms of the respiratory tract. Chronic cough of unknown origin, laryngeal complaints, throat discomfort, breathing disorders, bronchitis, pneumonia and even non allergic asthma, resistant to steroid therapy, are suspicious of being reflux related. Other symptoms are haematemesis, eructation, dysphagia, odynophagia, hiccups, changes in the oral, nasal and pharyngeal mucosa, dental erosions and cardiac problems. Laryngopharyngeal reflux (LPR) is present in up to 60% of GERD patients. Symptoms of this multifactorial syndrome are mainly extraesophageal, and are found in the head and neck region. The most common symptoms are cough, hoarseness, dysphonia, sore throat, globus pharyngeus, chronic postnasal drip, and Eustachian tube dysfunction, Some studies have shown that LPR has been associated with vocal cord polyps, vocal cord granulomas,

laryngospasm, subglottic stenosis and laryngeal carcinoma [55]. Esophagitis can be caused by reflux mechanism, infections, caustic agents, ionizing radiation, thermal injuries, eating disorders, medications, and as a part of some sistemic diseases. The most common symptoms are dysphagia and odynophagia, heartburn and acid regurgitation, haematemesis. Severe and prolonged vomiting and straining can results in tears in the mucous membrane of the esophagus. This condition is called Mallory-Weiss Syndrome. The main symptoms are hematemesis and melena, and in severe cases heavier bleeding may occur. Ribs and webs are the most common structural abnormalities of the esophagus. Most of them are asymptomatic, but can occasionally present with intermittent dysphagia to solids. They are associated with Zenker's diverticulum and Plummer-Vinson Syndrome which is classically a triad of dysphagia, iron-deficiency anemia, and esophageal webs. Esophageal rings are almost always associated with a hiatal hernia [56]. The esophagus is the most common site of acute foreign body obstruction. The clinical presentation varies from mild to extremely severe, and the most common symptoms are hypersalivation and odynophagia [57]. Esophageal perforation is a rare and potentially life-threatening condition most commonly caused by manipulations with medical instruments, forced strining and foreign bodies. The most common symptoms are odynophagia, chest pain, vomiting and shortness of breath, and in 70% of patients with perforation of the intrathoracic esophagus there are pleuromediastinum and palpable crepitus in the soft tissue of the neck and thorax. Caustic injuries of the esophagus are potentially one of the most challenging clinical situations in gastroenterology. Caustics and corrosives cause tissue injury by a chemical reaction. The severity of injury and the clinical presentation depends on several aspects: Concentration of the substance, amount ingested, duration of tissue contact, location of damage, and pH of the agent: hoarseness, stridor, dysphagia, odynophagia, hematemesis, epigastric pain. Short-term complications include perforation and death [58, 59]. Esophageal cancer is the sixth most common cause of cancer deaths worldwide. In the initial stage it usually shows no symptoms. The most common symptoms are dysphagia, chest pain, pressure or burning, heartburn, coughing or hoarseness, weight loss, bleeding, and hiccups. As can be seen, almost all esophageal diseases shows atypical and extraesophageal symptomatology. Due to proper and accurate diagnosis and treatment, the cooperation of a multidisciplinary team is required.

Acknowledgements

We would like to thank Ms. Mirna Brunčić for translating this text.

Conflict of interest

The authors have no conflict of interest.

Notes

The figure is from the author's own source.

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