REVIEW

Oral Pathology in Digestive Diseases

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Abstract

Correlations between alterations in the oral cavity and systemic conditions have been widely reported. A considerable number of gastrointestinal (GI) diseases of varied nature may produce lesions in the hard and soft oral tissues. Among the different types of manifestations of GI, oral lesions represent an important, if not a major component of the manifestation of these diseases. As a consequence, recognition and management of oral lesions accompanying the GI conditions, is mandatory for all clinicians, either gastroenterologists or dentists. The aim of this article is to underline useful data about the most common GI conditions (intestinal bowel diseases (IBD), gastroesophageal reflux, genetic diseases, malabsorption conditions, infections, metastatic tumors) and their link to oral pathology.

Keywords: oral pathology, gastrointestinal diseases, etiopathogenesis, epidemiology.

Rezumat

Corelațiile între patologia orală și diferitele boli sistemice, au fost raportate pe scară largă. Un număr considerabil de boli gastrointestinale (BGI), de diferite cauze, produc leziuni la nivelul țesuturilor dure și moi din cavitatea bucală. Printre diferitele modalități de manifestare ale BGI, leziunile orale ocupă un rol important, dacă nu chiar major, din punct de vedere al exprimării extradigestive a acestor boli. În consecință, recunoașterea și tratarea leziunilor orale care însoțesc BGI, reprezintă pași obligatorii pentru toți clinicienii, atât gastroenterologi cât și dentiști. Scopul acestui articol este de a sublinia informațiile cele mai utile privind BGI frecvent întâlnite (boala inflamatorie intestinală, boala de reflux gastroesofagian, bolile genetice, sindromul de malabsorbție, infecțiile, tumorile metastatice) și legătura lor cu patologia orală.

Cuvinte cheie: patologie orală, boli gastrointestinale, etiopatogenie, epidemiologie.

INTRODUCTION

Correlations between alterations in the oral cavity and systemic conditions have been widely reported[1-6]. Oral cavity can act as a mirror, which has the potential to reflect the human body's internal condition[7]. A considerable number of gastrointestinal (GI) diseases of varied nature (inflammatory, infectious, genetic and other etiology) may produce alterations in the hard and soft oral tissues[2-4]. Many GI diseases can give rise to different oral lesions. Sometimes, the oral lesions are similar to GI lesions, while at other times, the oral changes are caused by systemic alterations secondary to GI disease, such as those related to malabsorption[2]. These pathological manifestations are often misdiagnosed by both gastroenterologists and dentists. In this article we will focus on the most frequent gastrointestinal disorders that can be an etiologic factor for oral pathology. Among these are gastroesophageal reflux disease, inflammatory bowel diseases and some genetic diseases. Although the frequency of oral manifestations is variable across GI diseases and, in most cases are non-speci-

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fic, these disorders may precede the underlying disease and therefore can facilitate an early diagnosis[1-7]. The oral tissues may also offer an easy biopsy site for conditions such as inflammatory bowel diseases or digestive metastatic tumors. Careful and repeated assessment of the oral cavity is essential for a proper diagnosis[6-8].

ORAL LESIONS

1. Recurrent aphthous stomatitis (RAS)
It is a common disease of the oral mucosa, which occurs more frequently in children and young people, with an average incidence of between 20% and 60% over a lifetime[1-3]. RAS often begins in the second decade of life and reaches the highest frequency in the third decade. There are many variations in clinical patterns, such as frequency, duration, number and size of lesions. Usually the lesions are round or ovoid ulcerations with well-circumscribed margins, reddish halo, and yellow or gray bottom. Pain is the main symptom of RAS and often affects the quality of life of the patient and causes anxiety. Although trauma, stress, microorganisms, family history, food hypersensitivity, immunological factors, hormonal factors and genetic predisposition have been proposed as potential causal factors, the etiology of RAS is still unknown. It is reported that sleep disorder is also linked to immunological disorder[7-10]. Other predisposing factors include celiac disease and nutritional deficiencies: low levels of iron, vitamins B3 and B12, vitamin C and folic acid[10,11].

2. Labial swelling and fissuring:
It consists in a chronic enlargement of the lips with perpendicular fissures, cracks or crusts along the vermilion.

3. Cobblestoning:
The jugal mucosa exhibits normal color plaques separated by mild depressions or fissures, giving the appearance of cobblestones.

4. Mucogingivitis:
The gingival tissues may become hyperplasic and granular, not only the free gingiva but also the attached gingiva, and in certain cases this lesion can be extended up to the mucogingival margin.

5. Pyostomatitis vegetans (PV):
PV is described as a chronic muco-cutaneous pathology consisting of the formation of numerous pustules (intra and subepithelial abscesses) with white-yellow content and with an erythematous and edematous base[8-13]. These lesions look like a snail. The lesions are found on the tongue, lips, gums, tonsils, mouth, soft and hard palate.

6. Linear ulcerations:
These lesions are usually located in the buccal sulci and may be accompanied by hyperplastic mucosa at their borders.

7. Angular cheilitis:
The commissural and adjacent skin may have recurrent fissures and indurated erythematous plaques not necessarily related with Candida infection.

8. Dental enamel defects

9. Atrophic Glossitis
The filiform papilla and sometimes the fungiform papilla of the dorsum of the tongue undergo atrophy, leaving a bald, red tongue.

10. Caries
11. Herpetiform dermatitis
Dermatitis herpetiformis is an uncommon chronic skin disease that rarely affects the oral cavity. Oral manifestations include erythematous-purple macules, erosions, ulcers and blisters, which can affect the tongue, buccal mucosa and alveolar ridge. Clinically, it is difficult to make a differential diagnosis between diseases that produce vesicles, such as pemphigus or pemphigoid, celiac disease, so the histological and immunofluorescence studies are needed[6,7,14].

12. Other non-specific oral findings reported in literature include submandibular lymphadenopathy, sicca syndrome and hyposialia, dental caries, halitosis, candidiasis, dysphagia, odynophagia, lichen planus, dysgeusia, glossitis, mucosal discoloration, periodontal involvement, perioral erythema with scaling and minor salivary gland enlargement.

GASTROINTESTINAL DISEASES AND THEIR ORAL MANIFESTATIONS

1. Idiopathic inflammatory bowel disease (IBD)

The term inflammatory bowel disease (IBD) involves a group of chronic inflammatory disorders of not well-

known etiology that affects different segments of the gastrointestinal tract, mainly the bowel. The two main forms of IBD are Crohn's disease (CD) and Ulcerative Colitis (UC). The signs and symptoms are related to the damage in the bowel, but in some cases the patient can exhibit extra intestinal manifestations, also in the oral cavity, even before the intestinal manifestations are found. The clinical differences between the oral manifestations of CD and UD may be blurred with overlapping clinical features. Nonspecific clinical changes such as dry mouth, halitosis and gastric reflux are found and these changes are neither diagnostic nor helpful in the differentiation of the two conditions. The microscopic findings of granulomas are considered diagnostic of oral Crohn's disease, whereas micro-abscesses, containing neutrophils and eosinophils, without granulomas are considered typical for ulcerative colitis[8,9,12,13].

1.a. Crohn's disease (CD)

Patients with Crohn´s disease develop chronic inflammation and non-caseating granulomas in different parts of the gastrointestinal tract, especially in the distal ileum and colon. The most common signs and symptoms include diarrhea and abdominal pain, but some patients could experience extra-intestinal manifestations of the disease, involving eyes, joints, skin and mouth[10,11].

Epidemiology

CD usually affects males in their third decade of life; however, it can appear in a wide range of ages including young children. Its incidence varies depending on the age of the group studied, being higher in pediatric patients. Regarding to its prevalence, there are geographical differences, but it has been estimated between 319 and 322 cases per 100,000 habitants[10].

Etiopathogenesis

The exact cause and pathogenesis of CD are still not known. It has been postulated that genetically predisposed individuals would present an imbalance or deregulation of their immune response when exposed to different agents, such as environmental (stress, tobacco and diet) and microbiological (bacterial species) agents leading to the pro-inflammatory environment and tissue damage seen in this disease[7,11].

Oral manifestations

Oral lesions in CD are more frequent in young male patients and their prevalence can range from 20 to 50%. The predominant clinical presentation includes ulcers, papules and edema, while the most common sites affected are lips, gingiva and the vestibular sulci. It has been reported that oral lesions are of help in the diagnosis of systemic Crohn's disease. Some papers reported that only 0.5% of the patients with Crohn's disease have also oral manifestations. These patients were more likely to have also anal and esophageal lesions. There is a predilection for males and onset in youth. Patients with active CD have been reported to have a higher degree of oral lesions, but apparently, the type of them has no relationship with the disease activity and type of treatment. Different types can coexist in the same patient, and according to the absence or presence of granulomas formation in the histopathological study, these are classified into specific and non-specific lesions respectively. The specific oral lesions are labial swelling and fissuring, mucosal tags, cobblestoning, mucogingivitis, linear ulcerations. The nonspecific lesions are: recurrent aphthous stomatitis (RAS) like ulcerations, angular cheilitis, lichen planus, submandibular lymphadenopathy, sicca syndrome. Despite most of the oral manifestations of CD are not severe and their symptoms are mild or absent, some patients may experience facial distortion and disabling pain, originating emotional stress and deteriorating quality of life[1-3,10,11].

1.b Ulcerative colitis (UC)

It has clinical and histopathological features that differentiate it from CD: chronic inflammation of the gastrointestinal tract is mostly limited to the lining of the colon; there is no granuloma, the disease usually progresses with repeated periods of remissions and exacerbations and, in severe cases, can affect the entire thickness of the intestinal wall, which can cause significant bleeding[7,8,10].

Epidemiology

Ulcerative colitis is a favorite among men and is twice as common as CD. Unlike CD, UC is commonly diagnosed in patients with an average age of 30 years. The emergence of UC follows a bimodal model, with peaks in early adulthood and between the sixth and seventh decade of life. Europe is the continent with the highest incidence, with 24.3 new cases per 100,000 people every year[10].

Etiopathogenesis

Similar to CD, it is postulated that the development of UC would be influenced by different factors, including microbiological, genetic and environmental components that would interact with each other triggering the pathology.

Oral manifestations

Pyostomatitis vegetans (PV): is the oral counterpart of Pyoderma gangrenosum and is very commonly associated with UC and, unlike most oral lesions, is considered to be a specific marker of disease activity[8-13]. The patient may have fever, submandibular adenopathy and pain, extremely variable symptoms that are not necessarily related to the extent and size of the ulcers. Occasionally, oral manifestations may be the first indication that a patient has IBD10. Oral lesions should be routinely analyzed also by special histochemical investigations to rule out infectious etiology (e.g. fungal infections or tuberculosis). Because microscopic granulomatous lesions are observed in other diseases of the oral cavity, including orofacial granulomatosis and sarcoidosis, the positive diagnosis of Crohn's disease cannot be ruled solely by oral biopsy. However, oral biopsy can guide the specialist to investigate the GI tract for IBD[8-10]. The microscopic aspect itself is not diagnostic, because neutrophil or eosinophilic intraepithelial abscesses can be seen in other conditions, such as candidiasis, benign migratory glossitis, stomatitis areata migrans and pemphigus vegetans. Also, the clinical appearance and the anamnestic information should be correlated with the microscopic results. When present, the severity of the oral disease usually reflects the severity of the intestinal disease[11-13]. Furthermore, the gastroenterologist may use oral manifestations to determine the severity of bowel disease and / or response to treatment[1,11-13].

2. GENETIC DISEASES

2.a. Gardner syndrome

It is a genetic defect of chromosome 5 that leads to the disease by autosomal dominant or sporadic mutation characterized by intestinal polyposis with a very high risk of malignant transformation into colonic adenocarcinoma. It is associated with a number of extracolonic changes, including skin, skeleton and soft tissue. The potential manifestations of oral cavity are represented by: multiple enostoses of the jaws; supernumerary teeth and / or unerupted teeth; increased risk of odontomas; osteomas of the jaws and the paranasal sinuses. Enostoses are frequently observed radiographically in the alveolar portions of the jaws. They are completely asymptomatic. Supernumerary teeth appear in the region of the incisors, while the molar areas are rarely affected. The odontomas appear in the same distribution as the supernumerary teeth. Osteomas, which cause focal expansion of the surface of the maxillary bone, may be felt through the skin or buccal mucosa and may be large enough to be clinically visible[14-17].

2.b. Peutz-Jeghers syndrome

It is due to a mutation in the LKB1 gene. This condition, which is associated with hamartomatous polyposis, in most of the small intestine, is autosomal dominant or results from spontaneous mutation. The most significant oral manifestation is perioral and / or oral pigmentation, which develops from childhood. Oral lesions are usually flat, painless, brown, pigmented spots on the tongue or lip lining. Microscopically, these lesions show a slight acanthosis, with elongation of rete peg, and increased pigmentation of the adjacent melanocytes and keratinocytes, without an increase in the number of melanocytes. As with Gardner's syndrome, oral manifestations can help diagnose this condition at an early age and allow screening for intestinal disease[18].

3. HYPERSENSITIVITY

Celiac disease (CD) or „celiac sprue"

It is an autoimmune disease in which individuals who are genetically predisposed, show impairment of small bowel villi as a result of an abnormal immune response as a consequence of gluten ingestion. The diagnosis of CD is made clinically and histologically, which also allows the classification of this disease into four main types; classic, atypical, silent and latent. The diagnosis of CD can be sometimes difficult, mostly because patients may exhibit a wide spectrum of signs and symptoms. It is important to identify this disease process early because affected individuals have an increased risk for developing different malabsorption syndromes and lymphoma of the gut.

Etiopathogenesis

Gluten (present in most cereals) is partially degraded by the action of gastrointestinal enzymes in peptides that pass into the intestinal chorion due to increased permeability of the epithelial barrier. Once they reach the lamina propria, the peptides are cleaved by tissue transglutaminase, which increases their affinity for antigen presenting cells (APCs) and thus their immunogenicity. The presentation of these peptides to CD4+ lymphocytes triggers an adaptive immune response with inflammation and tissue damage due to the release of cytokines and matrix metalloproteinases[19].

Epidemiology

CD has been estimated to affect about 1% of the world's population, being increasing in recent years. Celiac disease is more common in European countries as well as in developing regions such as South America, South Asia and South Africa. Despite the typical occurrence in childhood, recent studies have reported an increase in adult involvement. Women are more affected than men (7: 1)[1,9,20,21].

Oral manifestations

Multiple oral manifestations were described. It is considered that 50% of patients with CD have no digestive symptoms at the time of diagnosis[19-24]. Moreover, oral lesions would be useful in the early detection of atypical CD, which corresponds to the most common form of this disease. These patients have an increased risk of enamel development abnormalities, especially enamel hypoplasia. In the temporal dentition, the most affected teeth are the second molar, while in the permanent teeth the central incisors are most commonly affected. In general, enamel hypoplasia is distributed bilaterally and symmetrically on both dental arches. Although lingual depapilation and burning sensation of the tongue have been described as typical oral manifestations of CD, these manifestations are less frequent. Often these manifestations are observed in patients with CD, secondary to anemia and not as a manifestation caused by the disease itself. It was found that in the active phase of the disease there was a decrease in salivary flow, which leads to dry mouth and burning sensation of the tongue. A higher rate of caries has been described in celiac patients. This cariogenic risk would be explained by the increased sensitivity of the hypoplastic enamel and the aforementioned changes in salivary flow rates and saliva composition observed in patients with CD. There is no consensus on the relationship between CD and mouth ulcers. RAS ulcers are likely to be secondary to anemia. Herpetiform dermatitis corresponds to a dermatological condition strongly associated with CD14.

4. INFECTION

Helicobacter pylori (Hp)

It is a Gram-negative aerophilic bacterium, which colonizes the gastric mucosa and its infection is associated with the development of gastric and duodenal ulcer, MALT lymphoma and gastric cancer. Although it has been suggested that *H. pylori* infection may be one of the etiological factors in the pathogenesis of RAS, this association is debatable. Hp might have a role in the pathogenesis of oral lesions, e.g. ulcers, carcinomas and lymphomas. Also, a dark erythematous tongue with slimy yellowish coating could be a sign of peptic ulcer due to Hp infection. On the other hand, it has been speculated that the oral cavity could be a second reservoir for Hp, and that is why the eradication treatment for Hp does not respond always properly. Hp can be found within the oral epithelium, such as buccal mucosa and the tongue. Hp was also found in normal or ulcerated/ inflammatory tonsils and in adenoid tissues[25-30].

5. OTHER PATHOLOGY

Gastroesophageal reflux disease (GERD)

It is a chronic digestive disorder caused by the return of gastric content to the esophagus and up or out of the oral cavity, with symptoms and, potentially, esophageal lesions. Gastric reflux is a normal process that occurs occasionally in children and adults. Most episodes are short and do not cause symptoms or complications. In contrast, people with gastroesophageal reflux disease have disturbing symptoms as a result of reflux. It is considered that at least 40% of the general population presents complaints, at least once a month. These are burns in the chest, which can extend to the neck and mouth, the regurgitation of ingested foods, sour or bitter taste, difficulties or pain when swallowed, vomiting, bloating, which occur more frequently after meals, with a duration of up to at 2 hours, being aggravated by the lying position and improved when standing up. It is important to note that atypical symptoms, such as dry cough, wheezing, hoarseness, can be confused with other airway diseases. The main cause for reflux disease is weakening of the lower esophageal sphincter. The most frequent oral lesions are: dental erosions, dysgeusia, sour taste, halitosis, mucositis, xerostomia, buccal epithelial atrophy, hyperesthesia, burning mouth, RAS like ulcerations. In patients with GERD, chronic or recurrent exposure to acidic gastric juice on tooth enamel can be recognized by the presence of dental erosion, the severity of which depends on the duration of the disease, the amount and quality of reflux and the individual resistance[31-34].

Plummer Vinson syndrome (PVS)

It is a rare clinical condition, characterized by a triad of dysphagia, iron deficiency anemia and esophageal web

in the post-cricoid region. Dysphagia is a common symptom. The dataon its prevalence and incidence are limited to a single population- based study (in South Wales in 1960). The oral lesions often found in PVS are related to iron deficiency anemia. Stomatitis, RAS likes ulcerations, angular cheilitis, pallor of the mucosa and atrophic glossitis are the most typical oral lesions[2,3,35].

Malabsorption syndrome

The malabsorption syndrome includes numerous clinical entities accompanied by chronic diarrhea, abdominal distension and failure to grow[2,7]. This may appear due to congenital defects in the membranous transport system of the small intestine epithelium or due to acquired defects of the surface of the absorption epithelium. GI diseases related to protein-caloric malnutrition, or micronutrient malabsorption may have an effect on the oral tissues. The iron malabsorption, inducing iron deficiency anemia, or the vitamin B12 malabsorption in pernicious anemia, are two of the most frequent example of malabsorption syndrome. When the malabsorption is sufficiently severe, the first oral manifestation is atrophic glossitis[36,37]. In milder cases, the atrophy is patchy. The more severe cases show involvement of the entire dorsum. In very severe cases, there may be shallow, round to oval-shaped, persistent ulcers with bright red borders, clinically resembling to the aphthous ulcers. Overt tongue lesions are usually sore, but a more common complaint is a burning sensation (glossopyrosis) that may precede clinically detectable oral lesions. Other involvements of the oral mucosal can show atrophic zones, with or without aphthous-like ulcers causing burning sensation, but these lesions are not as dramatic as the bald tongue. They often go unnoticed. Affected patients are predisposed also to angular cheilitis[36,37].

Metastatic tumors

The oral cavity is a rare but occasional target for metastases. Oral metastatic lesions from distant tumors are uncommon, accounting for only 1% of all oral malignancies[38-40]. The primary tumors are mainly lung, breast, kidney and colon tumors, which represent about 70% of the cases, reported in the literature[38-40]. Neoplasms of the gastrointestinal tract occasionally metastasize to the oral cavity, most commonly in the posterior mandible and usually through the blood stream. The veins of the vertebral plexus are considered the primary path. Patients with mandibular metastases may be asymptomatic, or may complain of jaw or tooth pain, paresthesia, or loosening of teeth. Initially, the tumor is sometimes found in an unhealed extraction socket, after an unexplained loosen tooth has been extracted. Radiographs are necessary and show irregular, poorly circumscribed and often multifocal opacities. Less commonly, metastases may involve the maxilla or oral soft tissues[38,41-42].

CONCLUSIONS

Among the different types of manifestations of gastrointestinal diseases, oral lesions represent an important, if not a major component of the manifestation of these diseases.

Although the frequency of oral manifestations, linked to gastrointestinal diseases, is variable and in most cases is non-specific (such as RAS like ulceration, stomatitis, burning sensation), these alterations may precede the underlying disease and therefore can facilitate an early diagnosis[2,3,7,43]. During the inspection of oral cavity, one can observe the persistent localized or generalized pain, halitosis, ptialism, xerostomia, the existence of ulcers (their type, frequency, recurrence, numbers, mass, or bleeding)[1,2,8]. This may increase the possibility of existing IBD, neoplasia, nutritional causes, infection, chronic inflammation, or gastroesofageal reflux[44]. According to the relationship between oral and digestive diseases the importance of recognition of oral signs and symptoms is a necessity. In many GI diseases oral lesions may be the only signs of the underlying disease and, therefore, the diagnosis can be confirmed only by recognizing the oral pathology[45]. The oral tissues offer a biopsy site for serious GI conditions such as IBD, or digestive metastatic tumors[46].

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References

1. Jajam M, Bozzolo P, Niklander S. Oral manifestations of gastrointestinal disorders. J Clin Exp Dent. 2017;9(10):e1242-8.
2. Daley TD, Armstrong JE. Oral manifestations of gastrointestinal diseases. Can J Gastroenterol 2007;21(4):241-249.
3. Mejia LM. Oral manifestations of gastrointestinal disorders. Atlas of the Oral and Maxillofacial Surgery Clinics of North America. 2017;25(2):93-104.
4. Rolands CM. Oral health presentations and considerations in gastrointestinal diseases. J Indian Acad Oral Med. 2015; 27(3):412-415.
5. Mantegazza C, Angiero F, Crippa R, Paglia M, Zuccotti GV. An overview on oral manifestations of gastrointestinal diseases. Italian Journal of Dental Medicine. 2018;3(4): 73-8.
6. Popovska M, Stavrova B, Atanasovska-Stojanovska A, Misevska P, Strezovska S, Kanurkova L, Gjurcheski J. Clinical oral manifestation in gastrointestinal disorders. Balk J Stom. 2011;15:41-47.
7. Amanat D, Zahedani SMZ. Oral manifestations of systemic diseases: a review. International Journal of Dental Clinics. 2013;5(1):13-19.
8. Vinesh E, Masthan K, Kumar MS, Jeyapriya SM, Babu A, Thinakaran M. A clinicopathologic study of oral changes in gastroesophageal reflux disease, gastritis, and ulcerative colitis. The Journal of Contemporary Dental Practice. 2016;17:943-947.
9. Muhvić-Urek M, Tomac-Stojmenović M, Mijandrušić-Sinčić B. Oral pathology in inflammatory bowel disease. World J Gastroenterol. 2016;22:5655-67.
10. Crippa R, Zuccotti GV, Mantegazza C. Oral manifestations of gastrointestinal diseases in children. Part 2: Crohn's disease, European Journal of paediatric dentistry. 2016;17(2):164-166.
11. Troiano G, Dioguardi M, Limongelli L, Tempesta A, Favia G, Giuliani M, et al. Can inspection of the mouth help clinicians diagnose Crohn's disease? A Review. Oral Health Prev Dent. 2017; 15(3):223-227.
12. Ponder A, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. Clin Epidemiol. 2013;5:237–247.
13. Katz J, Shenkman A, Stavropoulos F, Melzer E. Oral signs and symptoms in relation to disease activity and site of involvement in patients with inflammatory bowel disease. Oral Dis. 2003;9:34–40.
14. Patinen P. Oral findings in dermatitis herpetiformis and coeliac disease. Academic dissertation, ISBN 952-91-7347-4 (paperback), Helsinki 2004, 22-27.
15. Basaran G, Erkan M. One of the rarest syndromes in dentistry: gardner syndrome. European journal of dentistry. 2008; 2(3):208–212.
16. Cankaya AB, Erdem MA, Isler SC, Cifter M, Olgac V, Kasapoglu C, Oral CK. Oral and maxillofacial considerations in Gardner's Syndrome. International Journal of Medical Sciences. 2012; 9(2):137–141.
17. Pereira DL, Carvalho PA, Waddington Achatz MI, Rocha AC, TardinTorrezan G, Alves FA. Oral and maxillofacial considerations in Gardner's syndrome: a report of two cases. Ecancermedicalscience 2016;10:623.
18. Higham P, Alawi F, Stoopler ET. Medical management update: Peutz Jeghers syndrome. Oral Med Oral Pathol Oral Radiol Endod 2010;109:5-11.
19. Sedghizadeh PP, Shuler CF, Allen CM, Beck FM, Kalmar JR. Celiac disease and recurrent aphthous stomatitis: a report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94:474-8.
20. Pastore L, Carroccio A, Compilato D, Panzarella V, Serpico R, Muzio L. Oral manifestations of celiac disease. Journal of Clinical Gastroenterology. 2008;42(3):224-232.
21. Lahteenoja H, Toivanen A, Viander M, Maki M, Irjala K, Raiha I, Syrjanen S: Institute of Dentistry, University of Turku, Oral mucosal changes in coeliac patients on a gluten-free diet. Eur J Oral Sci Turku, Finland 1998;106):899–906.
22. Rashid M, Zarkadas M, Anca A, Limeback H. Oral manifestations of celiac disease: a clinical guide for dentists. J Can Dent Assoc 2011;77(39):1-6.
23. Macho V, Coelho AS, Veloso E, Silva DM, de Andrade D. Oral manifestations in pediatric patients with coeliac disease - a review article. The Open Dentistry Journal. 2017(11):539–545.
24. Wray D. Role of mucosal injury in initiating recurrent aphthous stomatitis. BMJ 1981; 283: 1569–1579.
25. Rubin JS, Benjamin E, Prior A, Lavy J. The prevalence of Helicobacter pylori infection in malignant and premalignant conditions of the head and neck. J Laryngol Otol. 2003;117: 118–21.
26. Leimola-Virtanen R, Happonen RP, Syrjänen S. Cytomegalovirus (CMV) and Helicobacter pylori (HP) found in oral mucosal ulcers. J Oral Pathol Med. 1995;24:14–7.
27. Cirak MY, Ozdek A, Yilmaz D, Bayiz U, Samim E, Turet S. Detection of Helicobacter pylori and its Cag A gene in tonsil and adenoid tissues by PCR. Arch Otolaryngol Head Neck Surg. 2003;129:1225–9.
28. Birek C, Grandhi R, McNeill K, Singer D, Ficarra G, Bowden G. Detection of Helicobacter pylori in oral aphthous ulcers. J Oral Pathol Med. 1999;28:197–203.
29. Czesnikiewicz-Guzik M, Loster B, Bielanski W, Guzik TJ, Konturek PC, Zapala J, et al. Implications of oral Helicobacter pylori for the outcome of its gastric eradication therapy. J Clin Gastroenterol. 2007;41:145–51.
30. Czesnikiewicz-Guzik M, Bielanski W, Guzik TJ, Loster B, Konturek SJ. Helicobacter pylori in the oral cavity and its implications for gastric infection, periodontal health, immunology and dyspepsia. J Physiol Pharmacol. 2005;56:77–89.
31. Ranjitkar S, Kaidonis JA, Smales RJ. Oral manifestations of gastroesophageal reflux disease. Journal of Gastroenterology and Hepathology. 2012;27:21-27.
32. Corrêa MC, Lerco MM, Henry MA. Study in oral cavity alterations in patients with gastroesophageal reflux disease. Arq Gastroenterol. 2008;45:132-6.
33. Ramachandran A, Raja Khan SI, Vaitheeswaran N. Incidence and pattern of dental erosion in gastroesophageal reflux disease patients. J Pharm Bioall Sci 2017;9 (Suppl):138-41
34. Warsi I, Ahmed J, Younus A, et al. Risk factors associated with oral manifestations and oral health impact of gastrooesophageal reflux disease: a multi-center, cross-sectional study in Pakistan. BMJ Open 2019;1-12.
35. Goel A, Bakshi SS, Soni N, Chhavi N. Iron deficiency anemia and Plummer–Vinson syndrome: current insights. Journal of Blood Medicine 2017;8:175–184.
36. Bohmer T, Mowe M. The association between atrophic glossitis and protein-calorie malnutrition in old age. Age Ageing. 2000;29:47–50.
37. Lupu VV, Burlea M, Ignat A, Ursu M, Paduraru G. Oral manifestations in the malabsorbtion syndrome. Romanian Journal of Oral Rehabilitation. 2017;9(4):48-51.
38. Tariqa H, Kamala MU, Mehershahia S, Saada M, Azama S, Kumara K, Niazib M, Makkera J, Myrta D. A rare case of colonic metastases from tonsillar carcinoma: case report and review of literature. World J Oncol. 2018;9(1):35-37.
39. Diaconu C, Mateescu D, Bălăceanu A, Marcu M, Jianu V, Stănică A. Pancreatic cancer presenting with paraneoplastic thrombophlebitis: a case report. Journal of Medicine and Life 2010; 3(1): 96-99.

40. Bălăceanu A, Diaconu C, Aron G. Budd-Chiari syndrome as an initial presentation of hepatocellular carcinoma – a case report. Medical Ultrasonography 2014;16(2):172-174.
41. Hirshberg A, Buchner A. Metastatic tumours to the oral region. An overview. European Journal of Cancer Part B: Oral Oncology. 1995;31(6):355-60.
42. Sánchez-Jiménez J, Acebal-Blanco F, Arévalo-Arévalo RE, Molina-Martínez M. Metastatic tumours in upper maxillary bone of esophageal adenocarcinoma. A case report. Med Oral Patol Oral Cir Bucal. 2005(10):252-7.
43. Ginghină O, Negrei C, Hudiță A, Ioana-Lavric V, Gălățeanu B, Dragomir S, Burcea Dragomiroiu GTA, Bârcă M, Nițipir C, Diaconu CC, Pantea Stoian AM, Iordache N, Bălănescu A. *In vitro* impact of some natural compounds on HT-29 colorectal adenocarcinoma cells. Farmacia 2017;65(6):947-953.
44. Dumitraș IC, Ionescu C, Bartoș D, Diaconu C. The diagnosis of malignant disease: sometimes a matter of pure chance. Arch Balk Med Union 2017;52(1):112-116.
45. Bălăceanu A, Diaconu C, Mateescu D, Stănică A. Hepatocellular carcinoma with hepatic and pulmonary metastasis, inferior vena cava and left pulmonary artery thrombosis in a patient with asymptomatic hepatitis C. Case report. Medical Ultrasonography 2010;12(4):345-348.
46 Diaconu C, Bălăceanu A, Costache C, Arsene D. A rare tumor revealed by abdominal trauma: case presentation. Journal of Gastrointestinal and Liver Diseases 2013;22(Supplement 1): 151.