ORAL MANIFESTATIONS OF THE CELIAC DISEASE. PART II. A REVIEW OF RARE ORAL FINDINGS

Gheorghe G. BĂLAN[1], Roxana NEMȚEANU[1], Eugeniu MIHĂLAŞ[2], Alina PLEŞA[1], Carmen SAVIN[1]

[1]M.D., PhD, „Grigore T. Popa" University of Medicine and Pharmacy of Iaşi, Romania
[3]D.M.D., PhD, „Grigore T. Popa" University of Medicine and Pharmacy of Iaşi, Romania

Corresponding author: Roxana Nemțeanu; e-mail: maxim_roxxxana@yahoo.com

Abstract

Celiac disease (CD) has become a relatively prevalent disease which associates systemic manifestations mainly conditioned by the dysimmune response triggered by gluten diet. Its oral manifestations have been proven to lead to health disparities and impaired quality of life. Such findings include mainly dental enamel defects (DEDs) and recurrent aphthous stomatitis (RAS). Nevertheless, there are also some potentially severe oral conditions associated with CD, considered to be rare, among which various oral cancers, atrophic glossitis or glossodynia. Thus, the aim of our study was to perform a systematic-review of case presentations reporting rare oral findings associated with CD. The searching protocol was applied to EMBASE, OVID and PubMed. Both pediatric and adult patients were included. The identified conditions include: Plummer-Vinson Syndrome, atrophic glossitis, glossodynia and some oral cancers. Therefore, dental practitioners should be ready to suspect CD also in such rare cases, as prompt management of such conditions could prevent severe and even life threatening complications.

Keywords: *glossodynia, periodontitis, oral cancer, malabsorption*.

1. INTRODUCTION

Celiac disease (CD) is a chronic inflammatory immune-allergic disease with a relatively high prevalence among both children and adults of up to 1% [1-3]. The chronic immune system activation triggers local enteric and systemic damages, many of the latter having a yet incompletely known path physiology. Many of the systemic manifestations of CD are described within the oral cavity, of which dental enamel defects (DEDs), recurrent aphthous stomatitis (RAS), dental caries (DC), aphthous ulcers (AU), and delayed eruption of teeth (DET) are considered the most frequent [4,5]. Such assumption has been confirmed by one of the previous studies developed by our team [6]. These can result in potentially severe complications, such as weight loss and malnutrition, chronic pain or even depression [7].

To date, extra digestive manifestations of numerous digestive diseases are reported and intensively studied in both adult and pediatric populations [8-10], as they could serve as markers for early diagnosis and proper management. Moreover, new insights towards alternative pathogenical roots of digestive diseases are studied, stress being laid on their systemic multi-organ manifestations [11,12].

Many authors report associations between CD and various conditions of the oral cavity, considered as rare. Given that CD has become a relatively common condition and due to the active role that dentists should have in facilitating its proper diagnosis, our paper aims at presenting a minireview of rare oral findings associated with CD.

2. MATERIALS AND METHODS

The minireview has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13], following a protocol established by the authors. PRISMA checklist and flow diagram have been used [14]. Given the topic of the research, the same search strategy and study selection methodology applied in our previous work has been used [6].

Search strategy

Publications covering the field of oral manifestations of CD were included in the systematic search. The review was limited to peer-reviewed publications, journal articles, books or chapters, and abstracts discussing the oral conditions associated with celiac disease. Unpublished or supplementary materials containing older or complementary data have not

been included. No limits were applied for language, and the foreign papers were translated into English. The majority of cases were reported in English, several included cases were reported also in Dutch, Spanish, French, German, Hebrew, Italian, Portuguese, Russian, and Polish.

Cases were identified by active keyword assessment within 3 biomedical databases: EMBASE, OVID and PubMed. Database screening was done during the 21st and the 28th of March 2020. Publication date limits have been set: 2000-2020. No supplementary approaches, such as hand searching of journals, checking reference lists, searching trials or court registries, contacting involved parties, or contacting authors, were performed. Search terms were selected from the Medical Subject Headings (MeSH) registry. Operator 'and' was used. We searched for the following keyword combination in all databases: 'oral manifestations and celiac disease'. No other search restrictions were applied.

Study selection and choice of outcomes

Study selection and eligibility assessment for systematic review were performed independently, according to an unblinded algorythm, by all authors. Disagreements were resolved by consensus. The standard process for selection included first assessment of relevance performed by the analysis of title, followed by title assessment. Subsequently, the data items required for review were searched within the full-text versions of the relevant publication. Studies published only in abstract and inaccessible full text versions, due to unknown language or inaccessible journal archive, were excluded. Within the eligible publications, inclusion and exclusion criteria for review were applied. Inclusion criteria consisted in: (a) study design: case presentation or presentation of a case series; (b) assessment of oral lesions associated with CD; (c) publication consistent with peer reviewed article. Exclusion criteria: (a) other types of observational and/or experimental study designs; (b) publications reporting oral manifestations considered as frequent: DEDs, RAS, DC, AU, and DET; (c) letters to the editor; (f) systematic reviews and meta-analyses. The remaining publications were referred to for systematic review. Flowchart of study selection is presented in Figure 1.

The searched outcomes within the case presentations or case series included rare oral findings in patients diagnosed with CD. We defined findings as rare by excluding the case presentations or case seried reporting on the otherwise frequent oral manifestations of CD, namely DEDs, RAS, DC, AU, and DET. Identification of such an oral condition led to the exclusion of the publication. Given the non-systematic character of such rare findings, no data abstraction or bias assessment is needed.

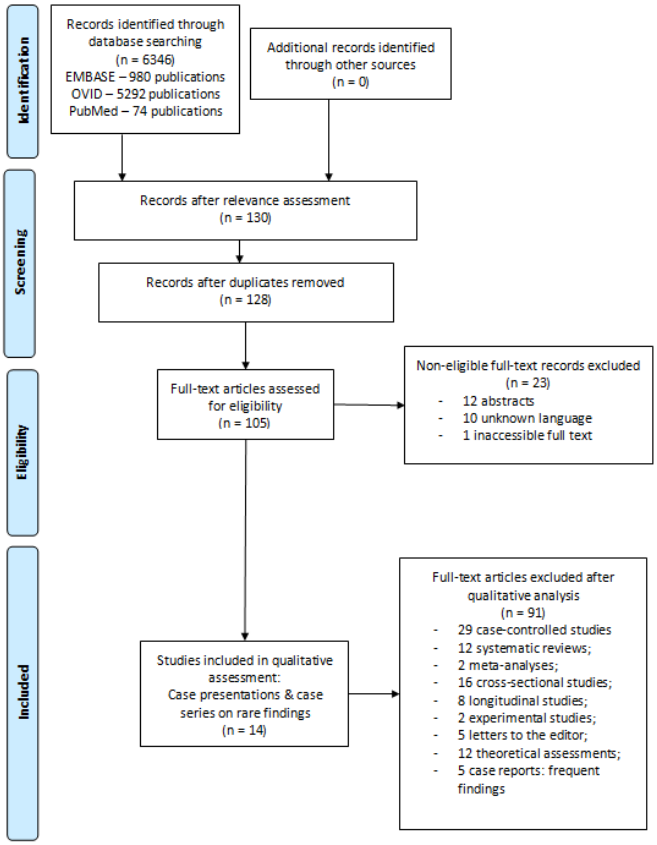

Fig. 1. Flowchart of the selected publications

3. RESULTS AND DISCUSSION

By implementing the search strategy, 6,346 publications were identified within the databases: original articles, books, chaperts, abstracts, posters, and letters, respectively 980 publications in EBSCO, 5,292 in OVID and 74 publications in PUBMED. After assessing their relevance by screening of title, 130 publications were selected. After adjusting for duplicates, 128 publications remained for full-text analysis, according to

inclusion and exclusion criteria. There were two articles with the same content identified within two different publicationns. Of the 128 remaining publications, 23 were excluded, due to absence of eligibility. The reasons for non-eligibility included mainly publication is abstract only (12 publications) or inaccessible language (10 publications). Studies published in Dutch, Italian, Hebrew, Portuguese, Polish and Russian have been excluded as non-eligible. One article was not accessible in full text and therefore excluded. Finally, 105 publications were included in the full-text assessment for implementing inclusion and exclusion criteria. Hence, 91 publications had to be further discharged, due to study design miss-match (as follows: 29 case-controlled observational studies,12 systematic reviews, 2 meta-analyses, 16 cross-sectional studies, 8 longitudinal studies, 2 experimental studies, 5 letters to the editor, and 12 theoretical assessments), and 5 case reports quoting frequent oral findings. The remaining 14 publications – case reports or presentations of case series on rare oral manifestations of CD – met all criteria for inclusion in meta-analysis. No unpublished relevant studies were selected.

Within the 14 selected publications listed in Table 1, 2 reported the association between Plummer-Vinson Syndrome and CD, 5 case reports presented cases of atrophic glossitis and glossodynia associated with CD, while the rest of 7 publications quoted several other oral manifestations – including mallignancies, birth anatomical deffects, Melkersson-Rosenthal Syndrome or Duhring's Disease found in CD patients.

Table 1. Main characteristics and findings of publications included in systematic review

Authors, Year	Source	Patient	Oral findings reported
Saroj et al., 2006 [15]	Esophagus. 2006;3(1):23-5	Adult	Plummer-Vinson Syndrome
Hefaiedh et al., 2013 [16]	Arab journal of gastroenterology: the official publication of the Pan-Arab Association of Gastroenterology. 2013;14(4):183-5	Adult	Plummer-Vinson Syndrome
Pastore et al., 2007 [17]	New England Journal of Medicine. 2007;356(24):2547	Adult	Atrophic glossitis
Erriu et al., 2012 [18]	Journal of medical case reports. 2012;6(1):1-3.	Pediatric	Atrophic glossitis
Bray et al., 2019 [19]	The Journal Of Family Practice. 2019;68(7).	Adult	Atrohpic glossitis and fissured tongue
Lucchese et al., 2012 [20]	Immunopharmacology and immunotoxicology. 2012;34(2):247-9.	Adult	Atrohpic glossitis and glossodynia
Mosaico et al., 2018 [21]	International Journal of Biomedical Science. 2018;14(1):41-47.	Pediatric	Localized necrotic ulceration gingivitis
Zinelabidine et al., 2012 [22]	Pan African Medical Journal. 2012;12(1).	Adult	Glossodynia
Singh et al., 2016 [23]	The Indian Journal of Pediatrics. 2016;83(6):598-9.	Pediatric	Ectopic erruption of permanent molars

Authors, Year	Source	Patient	Oral findings reported
Anokhina et al., 2020 [24]	BioNanoScience. 2020;10(1):311-4	Adult	Oral dermatitis herpetiformis (Duhring's disease)
Jessner et al., 2003 [25]	The American journal of gastroenterology. 2003;98(5):1208	Adult	Plummer-Vinson Syndrome, Postcricoid carcinoma, Tongue carcinoma
Dobros et al., 2018 [26]	Quintessence International. 2018;49(5).	Adult	Multiple invasive cervical resorption
Martins et al., 2019 [27]	BMJ Case Reports CP. 2019;12(8):e229857.	Adult	Melkersson-Rosenthal syndrome
Lima et al., 2008 [28]	Journal of the European Academy of Dermatology and Venereology: JEADV. 2008;22(9):1122-3.	Adult	Vulvovaginal gingival syndrome

Plummer-Vinson Syndrome and CD

Classical triad definition of Plummer-Vinson Syndrome includes the presence of dysphagia, iron-deficiency anemia and esophageal webs. The exact prevalence of the syndrome is not available, due to the extremely rare cases, most of whom are white middle-aged women [29]. Overlap between the syndrome and CD has been described in two case presentations [15,16], a clear common diagnostic feature being chronic iron-deficiency anemia. Despite its low prevalence, recognition of the syndrome is important because of the relatively increased risk of patients to develop squamous cell carcinoma of the esophagus [29]. Malapsorption could be frequently encountered in patients with dysphagia and therefore could delay the diagnosis of other possible concurrent causes, like CD of potentially subsequent mallignancies.

Atrophic glossitits, glossodynia and CD

Atrophic glossitis is an inflammatory confition of the tongue, featuring a smooth glossy appearance of the mucosa with an errithematous backgroung, frequently accompanied by glossodynia. Besides median rhomboid glossitis, fissured and geographic tongue, hairy tongue or leucoplakia, atrophic glossitis is most frequently associated with systemic diseases, among which CD, as well [30]. Other possible systemic diseases primary related to atrophic glossitis include amyloidosis, burns, candidiasis, malnutrition, sarcoidosis, Sjogren's syndrome systemic infections, psoriasis and vasculitis [18,30,31]. In many cases, the cause of tongue abnormalities remains unclear. Glossodynia could be the primary symptome of such underlying tongue conditions associated to systemic diseases. Remission of oral manifestations is expected to follow the specific therapy of the systemic trigger. However, routine screening for CD in patients with atrophic glossitis or glossodynia has not been established.

Oral cancers and CD

Presentation of CD can include a large variety of malignancies, among which the most frequent are considered to be non-Hodgkin lymphoma, squamous cell carcinoma of the esophagus, melanoma, and adenocarcinoma of the small bowel [32]. Squamous-cell carcinomas are the most frequent malignancies of the oral cavity. There have been cases of carcinomas of the tongue and cervical region in CD patients, but there is lacking evidence towards a pathogenical link.

Other rare findings

Rare findings associated with CD are cases of localized necrotic ulceration gingivits, multiple invasive cervical resorption, Melkersson-Rosenthal syndrome (triad of: recurrent orofacial edema, facial nerve palsy and fissured tongue), oral dermatitis herpetiformis (Duhring's disease), and the vulvovaginal gingival syndrome (a particular form of erosive lichen planus of the mucosae and vulvo-vaginal apparatus). All such mannifestations are extremely rare, even when not associated with CD.

4. CONCLUSIONS

CD is associated with a high variety of oral mannifestations, some of them frequent, others rare. Such abnormalities can represent an unclear condition for dentists. Despite their prevalence, dental practitioners should be ready to recognize potential associations and refer their patients to further work-up and differential diagnosis, especially when an idiopathic oral disorder is recorded. Nevertheless, multidisciplinary intervention with the involvemen of gastroenterologists, general practitioners or immunologists should be promoted in order to design best action plans for such patients.

References

1. Rewers M. Epidemiology of celiac disease: what are the prevalence, incidence, and progression of celiac disease? Gastroenterology. 2005;128(4):S47-51.
2. Mardini HE, Westgate P, Grigorian AY. Racial differences in the prevalence of celiac disease in the US population: National Health and Nutrition Examination Survey (NHANES) 2009–2012. Dig Dis Sci. 2015;60(6):1738-42.
3. Ludvigsson JF, Murray JA. Epidemiology of celiac disease. Gastroenterol Clin North Am. 2019;48(1):1-8.
4. Pastore L, Carroccio A, Compilato D, Panzarella V, Serpico R, Muzio LL. Oral manifestations of celiac disease. J Clin Gastroenterol. 2008;42(3):224-32.
5. Rashid M, Zarkadas M, Anca A, Limeback H. Oral manifestations of celiac disease: a clinical guide for dentists. J Can Dent Assoc. 2011;77(b39):1-6.
6. Nemteanu R, Balan GG, Mihalas E, Plesa A, Savin C. Oral Manifestations Of The Celiac Disease Part I. A Systematic Review Of Case-Controlled Studies. International Journal of Medical Dentistry. 2020;24(2):165-73
7. Krzywicka B, Herman K, Kowalczyk-Zając M, Pytrus T. Celiac disease and its impact on the oral health status-review of the literature. Adv Clin Exp Med. 2014;23(5):675-81.
8. Diaconescu S, Miron I, Gimiga N, Olaru C, Ioniuc I, Ciongradi I, Sarbu I, Stefanescu G. Unusual endoscopic findings in children: esophageal and gastric polyps: three cases report. Medicine (Baltimore). 2016;95(3):e2539.
9. Gimiga N, Bors AM, Stefanescu G, Iorga M, Diaconescu S. Effective communication and psychotherapy in reducing anxiety related to digestive endoscopy procedures for pediatric patients. International Journal of Medical Dentistry. 2016;20(4):255-60.
10. Gîlcă-Blanariu GE, Diaconescu S, Ciocoiu M, Ştefănescu G. New insights into the role of trace elements in IBD. Biomed Res Int. 2018;2018:1813047. doi: 10.1155/2018/1813047.
11. Maxim R, Pleşa A, Stanciu C, Gîrleanu I, Moraru E, Trifan A. Helicobacter pylori prevalence and risk factors among children with celiac disease. Turk J Gastroenterol. 2019;30(3):284-9.
12. Catinean A, Neag AM, Nita A, Buzea M, Buzoianu AD. Bacillus spp. spores—a promising treatment option for patients with irritable bowel syndrome. Nutrients. 2019;11(9):1968.
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. BMJ. 2009;151(4):W-65.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-41.
15. Saroj D, Naresh A, Puri AS. Atypical celiac disease with IgA deficiency presenting as Plummer–Vinson syndrome: a case report. Esophagus. 2006;3(1):23-5.
16. Hefaiedh R, Boutreaa Y, Ouakaa-Kchaou A, Kochlef A, Elloumi H, Gargouri D, Kharrat J, Ghorbel A. Plummer Vinson syndrome association with coeliac disease. Arab J Gastroenterol. 2013;14(4):183-5.
17. Pastore L, Muzio LL, Serpico R. Atrophic glossitis leading to the diagnosis of celiac disease. N Engl J Med. 2007;356(24):2547.
18. Erriu M, Canargiu F, Orrù G, Garau V, Montaldo C. Idiopathic atrophic glossitis as the only clinical sign for celiac disease diagnosis: a case report. J Med Case Rep. 2012;6(1):1-3.
19. Bray SC, Carek PJ. Red patches on the tongue with white borders, history of geographic tongue, incompletely treated celiac disease, Dx?. J Fam Pract. 2019;68(7):E9-E11.

20. Lucchese A, Guida A, Serpico R. Glossodynia and coeliac disease. Immunopharmacol Immunotoxicol. 2012;34(2):247-9.
21. Mosaico G, Sinesi A, Fanuli M, Casalino M, Mautarelli G, Casu C. Localized Necrotic Ulceration Gingivitis, in Orthodontic Patient, Treated with Non-Surgical Periodontal Therapy and with Probiotics (L. Reuteri). Int J Biomed Sci. 2018;14(1):41-7.
22. Zinelabidine K, Rhizlane I, Meziane M, Mernissi FZ. Aphtose buccale récidivante, et si c'était une maladie coeliaque. Pan Afr Med J. 2012;12:88.
23. Singh T, Bhatia HP, Sharma N. Glutened at the dental surgeon: celiac disease. Indian J Pediatr. 2016;83(6):598-9.
24. Anokhina AV, Silantyeva EN, Ruvinskaya GR. Clinical Case of Isolated Lesion of Oral Mucosa by Dermatitis Herpetiformis. BioNanoScience. 2020;10(1):311-4.
25. Jessner W, Vogelsang H, Püspök A, Ferenci P, Gangl A, Novacek G, Bodisch A, Wenzl E. Plummer-Vinson syndrome associated with celiac disease and complicated by postcricoid carcinoma and carcinoma of the tongue. Am J Gastroenterol. 2003;98(5):1208-9.
26. Dobroś K, Myciński P, Borowy P, Zarzecka J. Multiple invasive cervical resorption and celiac disease: A case report. Quintessence Int. 2018;49(5):407-412.
27. Martins JA, Azenha A, Almeida R, Pinheiro JP. Melkersson-Rosenthal syndrome with coeliac and allergic diseases. BMJ Case Reports CP. 2019;12(8):e229857.
28. De Lima AS, Werner B, Mukai MM, Giostri I, Santamaria JR. Vulvovaginal gingival syndrome and coeliac disease. J Eur Acad Dermatol Venereol. 2008;22(9):1122-3.
29. Novacek G. Plummer-vinson syndrome. Orphanet J Rare Dis. 2006;1:36. doi: 10.1186/1750-1172-1-36.
30. Reamy BV, Derby R, Bunt CW. Common tongue conditions in primary care. Am Fam Physician. 2010;81(5):627-34.
31. Joseph BK, Savage NW. Tongue pathology. Clinics in dermatology. 2000;18(5):613-8.
32. Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. Am J Med. 2006;119(4):355-e9.