

Long lasting atrophic glossitis due to autoimmune atrophic gastritis

Atrofični glositis kao prvi znak autoimunog atrofičnog gastritisa

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Summary

Autoimmune gastritis is a primary chronic inflammatory disease of the stomach mucosa caused by a pathologic autoimmune response directed against H/K -ATPase. Gastric lesions lead to sideropenic anemia due to iron malabsorption, megaloblastic anemia arising from vitamin B12 deficiency and atrophic glossitis, which may be the first and only clinical symptom. In everyday practice, tongue diseases are often misdiagnosed. A holistic approach, detailed history and examination may reveal underlying and interconnected diseases which are the main cause of the symptoms, presenting a significant challenge for the otorhinolaryngologist. The paper presents a 53- years old patient who was misdiagnosed with burning mouth mucosa syndrome

Key words: atrophic glossitis, autoimmune gastritis, megaloblastic anemia, holistic approach

Sažetak

Autoimuni gastritis je primarna kronična upalna bolest želučane sluznice uzrokovana patološkim odgovorom usmjerenim protiv H/K -ATP-aze. Želučane lezije dovode do razvoja sideropenične anemije uslijed malapsorpcije željeza, te megaloblastične anemije zbog deficijencije vitamina B12. Atrofični glositis može biti prvi i jedini znak bolesti. U svakodnevnoj kliničkoj praksi bolesti jezika često su pogrešno dijagnosticirane i predstavljaju izazov za otorinolaringologe. Sveobuhvatni pristup, detaljna anamneza i fizikalni pregled mogu razotkriti podležeće bolesti koje su međusobno ovisne i pravi uzrok tegoba. U radu je prikazana 53- godišnja bolesnica kod koje je pogrešno dijagnosticiran sindrom žarenja sluznice usta.

Ključne riječi: atrofični glositis, autoimuni gastritis, megaloblastična anemija, sveobuhvatni pristup

Med Jad 2023;53(3):293-298

Introduction

Oral status is often underestimated or misdiagnosed and inflammatory diseases of the oral cavity with different pathogenesis are treated by unwarranted antibiotic or symptomatic therapy. On the other hand, there are many oral manifestations of systemic diseases, in early and advanced stages. There are also many systemic manifestations including hematologic, gastroenterological,

neurologic and psychiatric aspects of the same disease.¹ In that sense, a holistic diagnostic and therapeutic approach leads to success in making the right decision in cases presenting with complex differential diagnoses.

Every clinician should carefully examine the head and neck status, especially oral mucosa for potentially important findings. We present a case of a silent, slowly progressive and unrecognized disease where only one clinical sign revealed an interesting cascade

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Received/*Primljeno* 2023-09-05; Revised/*Ispravljeno* 2023-11-17; Accepted/*Prihvaćeno* 2023-11-20

of interconnected findings leading to a diagnosis of autoimmune atrophic gastritis.

Case report

In 2021, a 53-year-old woman was referred to an otorhinolaryngologist by her family medicine practitioner due to burning mouth syndrome lasting for nine years. Her chief complaint was difficulty in eating certain types of food due to burning sensations and aches in her tongue and mouth. She also suffered paresthesia in the lower extremities, panic attacks, depression episodes and nausea. Her diet included vegetables and fruit shakes, avoiding lemon and cinnamon. For the past 25 years, she complained of sideropenic anemia because of menometrorrhagia, while gynecological disturbances were excluded. Numerous visits to different specialists during the years, ranging from hematologists, gastroenterologists, otorhinolaryngologists to oral pathologists revealed no underlying causes. After a detailed physical examination, we could suspect and trace the underlying disease back for several years.

Clinical examination showed an indurated, red and smoothed tongue with a pronounced central fissure and smoothed and red soft palate mucosa (Figure 1). Her medical history included chronic gastritis, sideropenic anemia due to menometrorrhagia lasting for twenty-five years, panic attacks, depression, previous thyroid surgery due to follicular adenoma. A comprehensive diagnostic approach to atrophic glossitis causes included laboratory tests which revealed macrocytosis without anemia, low levels of ferritin and eosinophilia. Microbiological analysis of the tongue swab showed no infections. A megaloblastic anemia due to vitamin B12 deficiency was diagnosed. A gastroenterologist was consulted and the patient underwent esophagogastroduodenoscopy revealing atrophic gastritis of the fundus and corpus of the stomach mucosa (Figure 2). A biopsy performed during endoscopy showed metaplastic epithelium and immunochromatographic detection of *Helicobacter pylori* presence was negative (Figure 3). To confirm the diagnosis of autoimmune gastritis, a laboratory test for antiparietal cell antibodies was performed and came back positive. Since the diagnosis was established, we did not perform sternal puncture seeking potential myelodysplastic syndrome. A neurologist was also consulted due to paresthesia of the lower extremities. Electromyoneurography findings showed a L5-S1 bilateral radiculopathy and axonal sensory polyneuropathy of the lower extremities due to demyelination of the sensory nerves caused by low levels of cyanocobalamin.

After the initial examination, we prescribed a polyvinylpyrrolidone — hyaluronic acid gel as a symptomatic relief which the patient used twice daily. She reported immediate improvement of the symptoms after two or three applications. When the diagnosis was established, treatment of atrophic glossitis included parenteral use of 1000 mcg of cyanocobalamin intramuscular injections every other day for the first week, once weekly for two months, and once monthly lifelong, respectively.

The patient showed complete resolution of the symptoms of atrophic glossitis in two weeks. Repeated oral examination showed no signs of glossitis revealing a normal architecture of the tongue and soft palate mucosa three months after the initial treatment (Figure 4). The psychological state of our patient improved successfully without the need for chronic therapy. Regular annually esophagogastroduodenoscopy will be needed because of the malignant potential of the disease.



Figure 1 Atrophic glossitis and the absence of filiform and fungiform papillae

Slika 1. Atrofični glositis i odsustvo filiformnih i fungiformnih papilla



Figure 2 Pale atrophic fundal mucosa with prominent blood vessels

Slika 2. Atrofična sluznica želuca s istaknutim krvnim žilama

Table 1 Patient key laboratory findings
Tablica 1. Ključni laboratorijski nalazi bolesnice

Parameter <i>Parametar</i>	Value <i>Vrijednost</i>	Unit <i>Jedinica</i>	Reference interval/ <i>Referentni interval</i>
Red blood cells/ <i>Eritrociti</i>	3.80 L	10 ¹² /L	3.86 - 5.08
Haemoglobin/ <i>Hemoglobin</i>	137	g/L	119 - 157
Haematocrit/ <i>Hematokrit</i>	0.414	L/L	0.356 - 0.470
MCV	108.9 H	fL	83.0 - 97.2
MCH	36.1 H	pg	27.4 - 33.9
MCHC	331	g/L	320 - 345
RDW	12.1	%	9.0 - 15.0
Platelets count/ <i>Trombociti</i>	247	10 ⁹ /L	158 - 424
MPV	9.6	fL	6.8 - 10.4
White blood cells/ <i>Leukociti</i>	6.79	10 ⁹ /L	3.4 - 9.7
Eosinophils/ <i>Eozinofili</i>	8.5 H	rel%	0 - 7
Basophils/ <i>Bazofili</i>	0.4	rel%	0 - 1
Neutrophils/ <i>Neutrofili</i>	45.9	rel%	44 - 72
Lymphocytes/ <i>Limfociti</i>	38.1	rel%	20 - 46
Monocytes/ <i>Monociti</i>	7.1	rel%	2 - 12
Glucose/ <i>Glukoza</i>	5.9	mmol/L	4.4 - 6.4
Creatinine/ <i>Kreatinin</i>	73	μmol/L	49 - 90
Glomerular filtration/ <i>Glomerularna filtracija</i>	82	mL/min/1.73m ²	>60
Bilirubin/ <i>Bilirubin</i>	10	μmol/L	3 - 20
AST	27	U/L	8 - 30
ALT	24	U/L	10 - 36
GGT	24	U/L	9 - 35
ALP	93	U/L	64 - 153
Alpha amylase/ <i>Alfa amilaza</i>	97 H	U/L	23 - 91
Fe	18	μmol/L	8 - 30
UIBC	42	μmol/L	26 - 59
TIBC	59	μmol/L	49 - 75
Ferritin/ <i>Feritin</i>	6 L	μg/L	9 - 136
Cyanocobalamine/ <i>Cijanokobalamin</i>	<109 L	pmol/L	138 - 652
Folic acid/ <i>Folna kiselina</i>	33.0	nmol/L	7.0 - 46.4
APCA	positive	titer / titar	neg.: < 1 : 40

*Abbreviations/*Kratice*: MCV – mean corpuscular volume/*prosječni volumen eritrocita*; MCH – mean corpuscular haemoglobin/*prosječni hemoglobin u eritrocitu*; MCHC – mean corpuscular haemoglobin concentration/*prosječna koncentracija hemoglobina u eritrocitu*; RDW – red cell distribution width/*širina distribucije volumena eritrocita*; MPV – mean platelet volume/*prosječni volume trombocita*; T. Bilirubin – total bilirubin/*ukupni bilirubin*; AST - aspartate aminotransferase/*aspartat aminotransferaza*; ALT – alanine aminotransferase/*alanin aminotransferaza*; GGT – gamma-glutamyl transferase/*gama glutamil transferaza*; ALP – alkaline phosphatase/*alkalna fosfataza*; Fe – ferrum/*željezo*; UIBC - unsaturated iron- binding capacity/*nezasićeni kapacitet vezanja željeza*; TIBC - total iron-binding capacity/*ukupni kapacitet vezanja željeza*; APCA - anti parietal cell antibodies/*antitijela na parijetalne stanice*

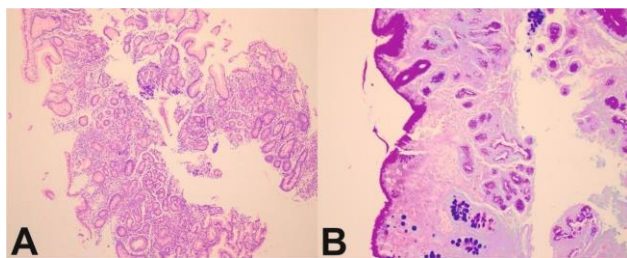


Figure 3 A) Microscopic appearance of gastric mucosa with reduced glandular structures and mononuclear inflammatory cells in lamina propria (HE×100), B) intestinal metaplasia in glandular epithelia (APAS×200).

Slika 3. A) Mikroskopski prikaz želučane sluznice reduciranih žljezdanih struktura i mononuklearnog infiltrata u lamini proprijji. (He×100), B intestinalna metaplazija u žljezdanom epitelu (APAS×200).



Figure 4 Three months after the beginning of treatment, a normal architecture of the tongue with filliform and fungiform papillae

Slika 4. Tri mjeseca od početka liječenja, normalna arhitektonika jezika s filiformnim i fungiformnim papilama

Discussion

Parietal cells are the largest and most complex cells in the gastric mucosa. They are found mostly within the middle third of the gastric glands of the body and fundus of the stomach. These cells are considered to be the source of hydrochloric acid and Castle's intrinsic factor as well as the rather large volume of water that accompanies active gastric secretion.² Such distribution and function are important in understanding the localization and nature of autoimmune gastritis which is restricted to body and fundus of the stomach.³ A combination of host and environmental factors are responsible for the onset of the disease.⁴ There is evidence, yet controversial, that *Helicobacter pylori* could induce autoimmune

gastritis through mechanisms of molecular mimicry and/or epitope spreading since Th1 cells cross react to certain peptides expressed both on the wall of *Helicobacter pylori* bacteria and H/K ATP-ase of parietal cells membranes. The gastric H/K-ATP-ase, a member of the P2-type ATP-ase family, is the integral membrane protein responsible for gastric acid secretion. The gastric H/K-ATP-ase is located in the canaliculus of the stimulated state and secretes gastric acid by an electroneutral ATP dependent hydrogen-potassium exchange.⁵ The transformation of these cells into antigen presenting cells activates the immunologic cascade reaction leading either to killing or apoptosis of the cells.⁶ Clearance of *Helicobacter pylori* infection with progression of gastritis to corpus atrophy suggests a major underestimation of its association with chronic atrophic gastritis.⁷ The associations with other autoimmune diseases led to further investigations and detection of HLA alleles DRB-1*3 and DRB-1*4 with predisposition to development of autoimmune gastritis.⁸ The incidence of gastric neoplasm is higher in patients with autoimmune gastritis compared to the general population.¹ Prospective studies have shown that 4-9% of patients with autoimmune gastritis, or its more severe form pernicious anemia, have gastric carcinoid tumors, whose frequency is 13-times higher than that of control subjects. In addition, autoimmune gastritis progression to atrophic gastritis, associated with intestinal metaplasia, may predispose to gastric adenocarcinoma in more than 10% of patients.⁹ Since gastric mucosa is atrophic, incompetent in producing an adequate amount of hydrochloric acid and intrinsic factor, there are no mechanisms of binding and transportation of exogenous cyanocobalamin from duodenum to terminal ileum and its absorption into circulation.¹⁰ This results in the lack of cyanocobalamin, a DNA synthesis precursor, leading to damaged erythropoiesis and release of immature macrocytes impotent to bind and transport oxygen to the cells causing manifesting megaloblastic anemia and atrophic glossitis.¹¹ Iron, which is reduced in the stomach by action of ascorbic acid cannot be absorbed because of atrophic mucosa leading to iron deficiency anemia, the first sign of megaloblastic anemia and autoimmune gastritis.¹⁰

Our patient had refractory iron deficiency anemia lasting for twenty-five years, caused by menometrorrhagia until menopause which was treated numerous times by parenteral or orally prescribed iron supplements. During that time, a gynecological examination showed no disease. Causes of vulvovaginal, cervical, uterine origin were excluded such as coagulopathies leaving menometrorrhagia, as a cause of chronic blood loss,

unclear. Hematological findings during that period included tongue examination which was described as red without atrophy but no further investigations were conducted. Cyanocobalamin, folic acid or antiparietal cell antibody laboratory tests were not ordered, so we could not exactly trace the time of origin of the disease. It can be assumed that iron deficiency anemia was a first sign of autoimmune atrophic gastritis. Autoimmune gastritis can have psychiatric manifestations due to B12 deficiency, such as psychosis or depression which were present in our patient for around 20 years. In accordance with that, chronic stress, as a manifestation of autoimmune gastritis, may be a cause of menometrorrhagia and iron deficiency anemia, solely, and in combination with poor iron absorption.¹²

Other etiology of atrophic glossitis includes deficiencies of some major nutrients besides B12 such as riboflavin, niacin, pyridoxine, folic acid, iron, zinc and vitamin E. Moreover, protein-calorie malnutrition, candidiasis, *Helicobacter pylori* colonization, xerostomia and diabetes mellitus are also the etiologies. Thyroglobulin antibody and thyroid microsomal antibodies are positive in patients with autoimmune gastritis connecting it to thyroid autoimmune diseases. Differential diagnosis includes migratory glossitis, rhomboid glossitis, black hairy tongue, candidiasis, lingua geographica and strawberry tongue.¹³

In cases of suspected atrophic glossitis, normal laboratory tests and without anemia should not exclude further investigation of cyanocobalamin or folic acid levels. In cases of normal laboratory findings, we should determine precursors of cyanocobalamin and folic acid — homocysteine and methylmalonic acid. A consultation with a gastroenterologist is necessary due to heightened gastric cancer risk and a hematologist in case of potential myelodysplastic syndrome.

Acknowledgment

This case report was presented online during the 12th congress of the Croatian Society of Otorhinolaryngology, Head and Neck Surgery and was published in *Medica Jadertina*, Vol.51, No. Supplement, 2021 as an abstract.

References

1. Minalyan A, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: current perspectives. *Clin Exp Gastroenterol* 2017;10:19-27.
2. Rohrer GV. Human gastric mucosa: correlation of

- structure and function. *Am J Clin Nutr* 1971;24:137-43
3. Kulnigg-Dabsch S. Autoimmune gastritis. *Wien Med Wochenschr* 2016;166:424-430.
4. Rodriguez-Castro KI, Franceschi M, Miraglia C, et al. Autoimmune diseases in autoimmune atrophic gastritis. *Acta Biomed* 2018;89:100-103.
5. Shin JM, Munson K, Vagin O, Sachs G. The gastric HK-ATPase: structure, function, and inhibition. *Pflugers Arch* 2009;457:609-22.
6. D'Elcios MM, Appelmelk BJ, Amedei A, Bergman MP, Del Prete G. Gastric autoimmunity: the role of *Helicobacter pylori* and molecular mimicry. *Trends Mol Med* 2004 ;10:316-23
7. Toh BH, Chan J, Kyaw T, Alderuccio F. Cutting edge issues in autoimmune gastritis. *Clin Rev Allergy Immunol* 2012;42:269-78.
8. Lahner E, Spoleitini M, Buzzetti R, et al. HLA-DRB1*03 and DRB1*04 are associated with atrophic gastritis in an Italian population. *Dig Liver Dis* 2010;42:854-9
9. Bizzaro N, Antico A, Villalta D. Autoimmunity and Gastric Cancer. *Int J Mol Sci* 2018 ;19:377
10. Atrah HI, Davidson RJ. Iron deficiency in pernicious anaemia: a neglected diagnosis. *Postgrad Med J* 1988;64:110-111.
11. Das KC, Das M, Mohanty D. et al. Megaloblastosis: from morphos to molecules. *Med Princ Pract* 2005;14 Suppl 1:2-14
12. Miceli E, Brondino N, Lenti MV. et al. Impaired Quality of Life in Patients with Autoimmune Atrophic Gastritis. *Dig Dis Sci* 2021;66:3322-3329.
13. Chiang CP, Chang JY, Wang YP, Wu YH, Wu YC, Sun A. Atrophic glossitis: Etiology, serum autoantibodies, anemia, hematinic deficiencies, hyperhomocysteinemia, and management. *J Formos Med Assoc* 2020;119:774-780

