Clinical Case Report

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An uncommon case of herpetic esophagitis in a small child with allergic rhinitis

A case report and literature review (CARE compliant)

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Abstract

Rationale: Herpetic esophagitis (HE) is a common condition in immunosuppressed patients, but a rare entity in immunocompetent patients affecting especially male teenagers and young adults.

Patient concerns: We report the case of a 5-year-old male patient, with a history of allergic rhinitis admitted in our clinic for acute onset fever refractory to antipyretics, chest pain, anorexia, refusal of solid food, accepting only small amounts of fluids, odynophagia, and epigastric pain. The clinical exam revealed severe malaise, pallor, decreased skin turgor, abdominal epigastric tenderness, heartburn at palpation within the epigastric area. The laboratory tests showed leukocytosis, monocytosis, hypoglycaemia, and elevated inflammatory biomarkers.

Diagnoses: The serology tests for human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV) were negative, except for immunoglobulin G (IgG) anti-EBV which was positive. The chest radiography was normal, and the abdominal ultrasound showed abdominal bloating. The upper digestive endoscopy revealed friable esophageal mucosa, with multiple ulceration on the entire esophagus, and whitish exudates especially on the middle and lower part of the esophagus suggesting a possible eosinophilic esophagitis or caused by Candida. Despite the empirical initiated treatment, the patient's evolution was only slowly favorable. The histological exam established the diagnosis of HE.

Interventions: We initiated acyclovir therapy with an outstandingly favorable evolution.

Outcomes: After 1 month, we detected the seroconversion of IgG anti-HSV. The patient's follow-up revealed no additional complaints.

Lessons: Despite its rarity in immunocompetent individuals, HE must be taken into account even in otherwise healthy small children. Allergic conditions might represent a predisposing factor for HE.

Abbreviations: CMV = cytomegalovirus, CRP = C-reactive protein, EBV = Epstein-Barr virus, ESR = erythrocyte sedimentation rate, Glu = glucose, HE = herpetic esophagitis, HIV = human immunodeficiency virus, HSV = herpes simplex virus, Ig = immunoglobulin.

Keywords: allergic rhinitis, child, esophagitis, herpes infection, predisposing factor

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Table of Contents Summary: Herpetic esophagitis (HE) is a common condition in immunosuppressed patients, but a rare entity in immunocompetent patients affecting especially male teenagers and young adults.

Consent to publish: Verbal and written informed consent was obtained from the patient's mother (legal guardian) for the publication of this case presentation.

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1. Introduction

Herpetic esophagitis (HE) was described for the first time in 1940 by Johnson, while its histopathologic description was provided 3 years later by Pearce et al.[1,2] Even though esophagitis is most often caused by gastroesophageal reflux, the esophagus is the most frequently affected visceral organ by herpes simplex virus (HSV) infection.[3] In a series of autopsies, HE was found to have an incidence of 1.8%.[4] It is well-documented that HE usually affects immunocompromised or severely ill hosts, defined as an opportunistic infection diagnosed especially in human immunodeficiency virus (HIV)-patients, those with underlying malignant disorders, burns, immunosuppressant drugs or systemic steroids, burns, or organ recipients.[3] HSV-1 is more commonly involved in HE than HSV-2 which may be incriminated only occasionally.[5] Nevertheless, concomitant oropharyngeal and genital lesions were reported in up to 20% of the cases diagnosed with HE.[6] The condition may be a result of viral reactivation, but more often is due to the local spread of the virus from a pharyngeal or an orolabial focus, being defined as a primary infection.[3] Several factors that lead to the disruption of normal esophageal mucosa barrier, such as gastroesophageal reflux and esophageal instrumentation, have been reported to predispose immunocompetent hosts to the development of HE.[7] Another hypothesis has also been postulated consisting in the transmission from an individual with HSV skin lesions, which was confirmed in approximately 20% of the patients diagnosed with HE.[6,8] This condition affects predominantly men, with a male to female ratio of 3:1.[9]

It has been proved that the esophagus is an immunologically active organ that may trigger an immune response to a wide range of stimuli.[10] Thus, for example the esophageal infiltration with eosinophils, formerly considered to be associated with gastroesophageal reflux is now defined as a hallmark of eosinophilic esophagitis.[10] Nevertheless, the esophageal epithelium lacks the secretory and absorbent functions, and expresses an insignificant amount of resident immunologic or lymphoid cells.[10] On the other hand, infective esophagitis is a rare entity and it usually occurs in predisposed hosts.

The diagnosis must be based on clinical symptoms, upper digestive endoscopy findings, histology and/or culture, but HSV serology may be another useful marker for the positive diagnosis. The clinical manifestations include unspecific prodromal symptoms such as high fever, loss of appetite, malaise, or weight loss,[11] and the acute period including upper digestive symptoms consisting in odynophagia, heartburn, and fever.[12] Other symptoms such as chest pain, dysphagia for both solids and liquids, and vomiting were also reported in the literature.[13] The upper digestive endoscopy may reveal a friable esophageal mucosa, multiple coalescent ulcerations of different sizes and depth presenting a volcano-like aspect that may resemble to a severe peptic esophagitis if present in the distal part of the esophagus.[8] Moreover, whitish exudates can also be noticed during upper digestive endoscopy in these patients resulting a possible confusion with esophagitis caused by candida or cytomegalovirus (CMV), but also eosinophilic esophagitis.[6,14] The histological exam confirms the diagnosis of HE providing particular cytopathological and immunohistochemically characteristics including the presence of multinucleated giant cells and eosinophilic intranuclear inclusions also known as Cowdry type A inclusions,[8,15] or ground glass inclusions.[9] While in immunosuppressed patients, the treatment with acyclovir is clearly established, in immunocompetent individuals it has triggered multiple controversies due to the self-limiting pattern of this condition lasting usually for up to 2 weeks. The complications of HE, such as upper gastrointestinal bleeding or esophageal perforation are extremely rare.[6,15] Nevertheless, gastrointestinal bleeding may be caused also by other conditions, such as different drugs,[16,17] or even *Helicobacter pylori* infection.[18]

We report this case in order to underline the occurrence of HE in an otherwise immunocompetent preschool aged child known with allergic rhinitis.

Informed consent was obtained from the patient's mother (legal guardian) for the publication of this case presentation.

2. Case presentation

2.1. Presenting concerns

We report the case of a 5-year-old male patient admitted in our clinic for acute onset fever refractory to antipyretics, chest pain, anorexia, refusal of solid food, accepting only small amounts of fluids, odynophagia, and epigastric pain. The symptoms appeared approximately 3 days before the admission in our clinic, and his general practitioner recommended treatment with Penicillin, but without any improvements. Therefore, after 2 days, the patients were admitted in the regional hospital where he was administered intravenously treatment with cephalosporin, proton pump inhibitors, and antipyretics, but the symptoms persisted being referred to our clinic for further investigations. We must mention that the patient and mother denied the possibility of any ingestion of corrosive agent. His personal history revealed a diagnosis of allergic rhinitis since the age of 2 years.

2.2. Clinical findings

The clinical exam at the time of admission revealed severe malaise, pallor, decreased skin turgor, abdominal epigastric tenderness, heartburn at palpation within the epigastric area. The patient weighed 17 kg.

2.3. Diagnostic focus and assessment

The complete cellular blood count at the time of admission revealed mild leukocytosis (Leu 12,360/μL) with monocytosis (Mo 1630/μL). We also found hypoglycemia (Glu 54 mg/dL) and increased inflammatory biomarkers (CRP 41.32 mg/L, ESR 50 mg/L). The blood culture was negative. We also performed serology tests for HIV, CMV, Epstein-Barr virus (EBV), and HSV, both IgM and IgG, and we found only IgG anti-EBV to be positive. The thoracic radiography did not reveal any pathological changes, while the abdominal ultrasound showed only abdominal bloating. The cardiology exam pointed out patent foramen ovale without clinical significance. We performed an upper digestive endoscopy which revealed friable esophageal mucosa, with multiple ulceration on the entire esophagus, and whitish exudates especially on the middle and lower part of the esophagus (Figs. 1 and 2). Based on all these findings, we raised the suspicion of eosinophilic esophagitis or caused by Candida with a possible superinfection.

2.4. Therapeutic focus and assessment

We initiated empirical treatment with Fluconazole and we continued the antibiotic treatment by vein. We also administered

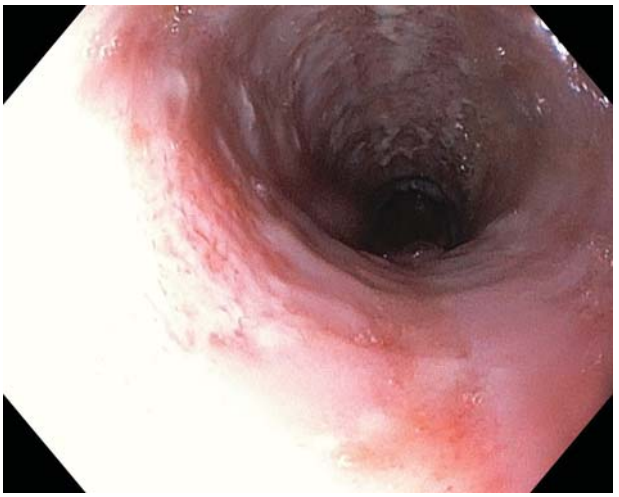

Figure 1. Endoscopic aspect of esophageal mucosa with whitish exudates.

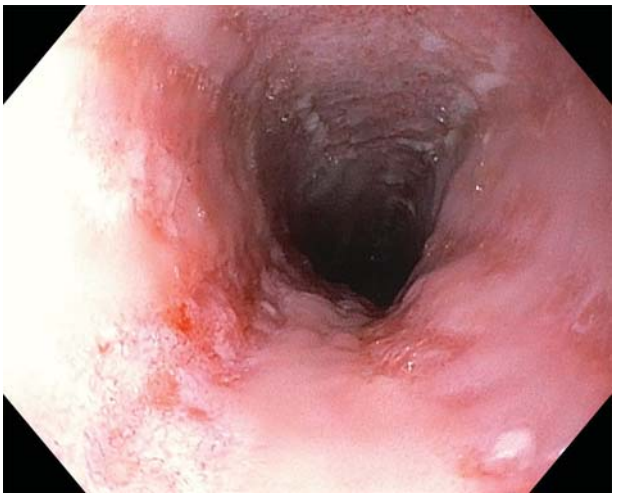

Figure 2. Endoscopic aspect of the friable esophageal mucosa with linear ulcerations.

proton pump inhibitors, analgesics, antipyretics, glucose, and electrolytes by vein for rehydration. The patient's evolution was slowly favorable. The histology of the esophageal biopsy specimens pointed out specific changes for herpetic esophagitis (Figs. 3 and 4). Therefore, we initiated treatment with acyclovir for 5 days with outstandingly favorable evolution.

2.5. Follow-up and outcome

After approximately 1 month, the patient's evolution was good, without any complaints. We repeated the serology for HSV and we found seroconversion of IgG anti-HSV. The rest of the laboratory parameters were within normal ranges.

3. Discussions

HE is a well-known opportunistic infection, but at the same time it is an uncommon condition in immunocompetent patients, affecting especially teenagers and young adults. Nevertheless, our case described HE in a very small child, a 5-year-old boy. Nevertheless, in a review of the literature performed by Canalejo Castrillero et al[13] who identified 53 cases of HE in immunocompetent individuals, the youngest patient was 14 years old, while the oldest was 82 years old. Moreover, a very old case report describes a case of HE in a younger patient, a healthy 8-year-old boy.[19] This condition is more frequent in men as it was also shown by the previously mentioned review which

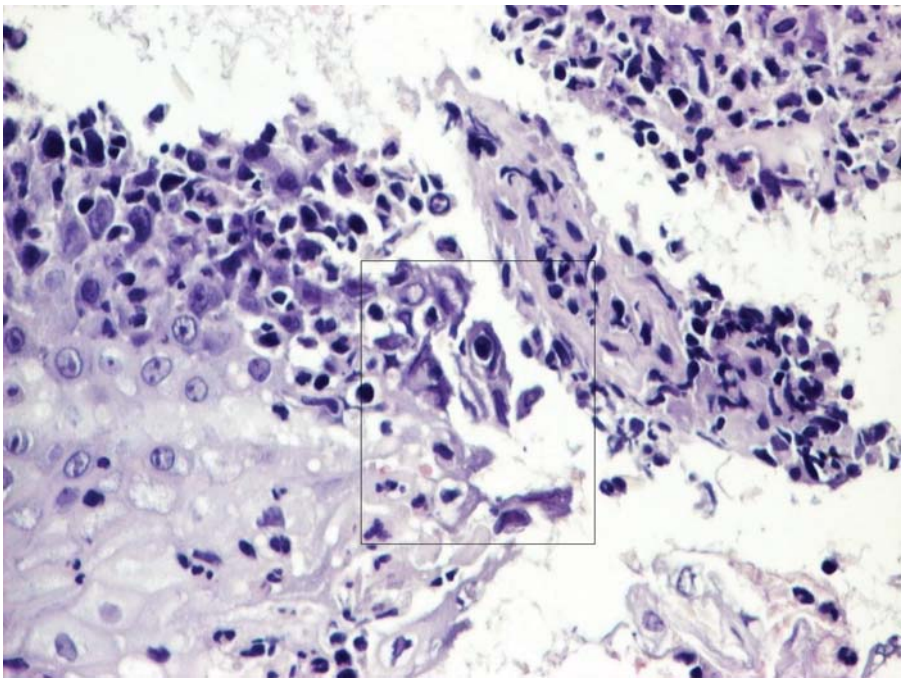

Figure 3. Histological exam—infected cells with pseudo-inclusions, and multinucleated giant cells.

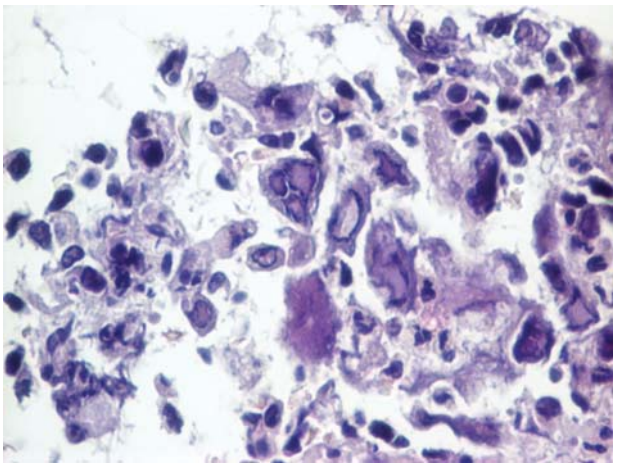

Figure 4. Histological exam—infected cells with Cowdry type A or ground glass inclusions.

pointed out that out of all 53 cases of HE, 39 were men and 17 were women.[13] Similarly, our case was also a man. The incriminated predisposing factors in immunocompetent hosts include gastroesophageal reflux, esophageal instrumentation, contact with a person who carries HSV skin lesions.[6–8] This latter theory was also found by Canalejo Castrillero et al[13] with an incidence of 14.3% in all assessed cases. Moreover, Lambert also confirmed this theory in his case report where the patient's mother and 6-year-old brother presented a history of recurrent herpes labialis.[19] Despite all these findings, neither our patient nor his family had any history of herpes infection. Childhood obesity, a well-known risk factor for gastroesophageal reflux reached alarming rates worldwide. Due to the wide spectrum of complications that may be associated with this nutritional disorder, among which HE, obesity screening, similar to other severe disorders[20] would be a useful prophylactic tool especially in genetically predisposed children.[21–28]

Regarding the clinical picture, HSV infection can range from asymptomatic to fatal conditions. A sudden onset of a triad comprising odynophagia, heartburn, and fever, without any obvious cause in an otherwise healthy individual should raise the suspicion of HE.[11] Other common symptoms are retrosternal pain, fever, cough, sore throat, herpetic orolabial or skin lesions, while less frequent ones include epigastric pain, vomiting, and diarrhea.[13] Nevertheless, a thorough anamnesis relies mostly on the pediatrician's communications skills.[29] Our patient presented both common symptoms, such as fever, odynophagia, and chest pain, but he also expressed uncommon ones like epigastric pain. Upper digestive endoscopy with histology of the esophageal biopsy specimens establishes the diagnosis in most of the HE cases. The most common endoscopic findings consist in extensive involvement of the esophageal mucosa, friability of the mucosa, variable size, and depth coalescent ulcerations and whitish exudates.[6,8] HE usually affects the middle and distal part of the esophagus, but in approximately 15% of the cases it may extend to the entire esophagus.[11] Moreover, in approximately 2% of the patients HE may concomitantly involve the stomach as well.[30] Similarly to the majority of reported cases, our patient presented impairment of the middle and lower part of the esophagus with friable esophageal mucosa, multiple ulcerations, and whitish exudates, but no involvement of the stomach. Histological examination of the esophageal biopsy specimens established the diagnosis in most of the cases of HE, but virologic culture is another commonly used method for the confirmation of the diagnosis. Moreover, serology for HSV may also be useful to detect the primary infection as a result of seroconversion.[11] In our case the histology exam established the diagnosis of HE showing an increased number of intraepithelial lymphocytes, rare neutrophils and eosinophils, degenerated cells, with amorphous aspect nuclei, with pseudo-inclusions. Moreover, the seroconversion of IgG anti-HSV after 1 month sustained the diagnosis of HE.

The presence of an increased amount of eosinophils within the esophageal epithelium can be triggered by different food or aeroallergens leading to eosinophilic esophagitis.[9] Recent studies focused on establishing a relationship between HE and eosinophilic esophagitis.[10,31,32] It is well-documented that patients with a history of allergy are more predisposed to developing eosinophilic esophagitis.[9] Our patient presented a history of allergic rhinitis, and therefore our initial suspicion was of eosinophilic esophagitis. Nevertheless, our case may suggest that allergic rhinitis might be a predisposing factor for HE.

The indication of acyclovir treatment is not well-established currently, but it should be taken into account in order to shorten the recovery periods and prevent potential complications.[31] Even though possible HE complications are rare, they can be life-threatening and include upper digestive hemorrhage (5.3%)[8,15,30] and esophageal perforation.[30,33] In our case, we decided to initiate acyclovir treatment despite the patient's lack of immunosuppression based on the severe endoscopic findings and the persistence of the symptoms, and fortunately our patient did not develop any complications.

To our best knowledge, this is the youngest patient diagnosed with HE reported in the literature until know.

4. Conclusions

HE is a rare entity in immunocompetent hosts. Recently, a hypothesis between allergic conditions, eosinophilic, and herpetic esophagitis has been postulated suggested also by our case. Even though HE affects predominantly adolescent and adults, small children may also represent rare targets of this condition.

Author contributions

Cristina Oana Mărginean, Lorena Elena Melit, and Maria Oana Mărginean conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Simona Mocan and Cristian Dan Mărginean designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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References

[1] Johnson HN. Visceral lesions associated with varicella. Arch Pathol 1940;30:292–307.
[2] Pearce J, Dagradi A. Acute ulceration of the esophagus with associated intranuclear inclusion bodies. Report of four cases. Arch Pathol 1943;35:889–97.
[3] Buss DH, Scharyj M. Herpesvirus infection of the esophagus and other visceral organs in adults. Incidence and clinical significance. Am J Med 1979;66:457–62.
[4] Itoh T, Takahashi T, Kusaka K, et al. Herpes simplex esophagitis from 1307 autopsy cases. J Gastroenterol Hepatol 2003;18:1407–11.
[5] DiPalma JA, Brady CE. Herpes simplex esophagitis in a nonimmunosuppressed host with gastroesophageal reflux. Gastrointest Endosc 1984;30:24–5.
[6] Ramanathan J, Rammouni M, Baran J, et al. Herpes simplex virus esophagitis in the immunocompetent host: an overview. Am J Gastroenterol 2000;95:2171–6.
[7] Pazin GJ. Herpes simplex esophagitis after trigeminal nerve surgery. Gastroenterology 1978;74:741–3.
[8] Kato S, Yamamoto R, Yoshimitsu S, et al. Herpes simplex esophagitis in the immunocompetent host. Dis Esophagus 2005;18:340–4.
[9] Marinho AV, Bonfim VM, Alencar D, et al. Herpetic Esophagitis in Immunocompetent Medical Student. Case Reports in Infectious Diseases. doi:10.1155/2014/930459.
[10] Monsanto P, Almeida N, Cipriano M, et al. Concomitant herpetic and eosinophilic esophagitis - a causality dilemma. Acta Gastroenterol Belg 2012;75:361–3.
[11] De la Riva S, Munoz-Navas M, Rodriguez-Lago I, et al. Herpetic esophagitis: presentation in an immunocompetent adolescent. Rev Espanolade Enfermedades Dig 2012;104:214–7.
[12] Lopes S, Macedo G, Veloso F. Herpetic esophagitis in immunocompetent individuals. J Port Gastroenterol 2006;10:355–8.
[13] Canalejo Castrillero E, García Durán F, Cabello N, et al. Herpes esophagitis in healthy adults and adolescents: report of 3 cases and review of the literature. Medicine (Baltimore) 2010;89:204–10.
[14] Khlevner J, Beneri C, Morganstern JA. Wrestling and herpetic esophagitis. Pediatr Infect Dis J 2011;30:911–2.
[15] Domínguez Alcón L, Pita Fernández L, Carretero L. [Herpes simple esophagitis in immunocompetent adult]. Rev Espanola Enfermedades Dig 2009;101:368–9.
[16] Melit LE, Mărginean CO, Mocanu S, et al. A rare case of iron-pill induced gastritis in a female teenager: a case report and a review of the literature. Medicine (Baltimore) 2017;96:e7550.
[17] Mărginean MO, Melit LE, Mocanu S, et al. Ibuprofen, a potential cause of acute hemorrhagic gastritis in children - a case report. J Crit Care Med (Targu Mures) 2018;4:143–6.
[18] Mărginean MO, Mărginean CO, Melit LE, et al. The impact of host's genetic susceptibility on Helicobacter pylori infection in children. Medicine (Baltimore) 2017;96:e7612.
[19] Lambert H, Eastham EJ. Herpes oesophagitis in a healthy 8 year-old. Arch Dis Child 1987;62:301–2.
[20] Zerjav Tansek M, Groselj U, Angelkova N, et al. Phenylketonuria screening and management in southeastern Europe - survey results from 11 countries. Orphanet J Rare Dis 2015;10:68.
[21] Mărginean C, Mărginean CO, Bănescu C, et al. Impact of demographic, genetic, and bioimpedance factors on gestational weight gain and birth weight in a Romanian population: a cross-sectional study in mothers and their newborns: the Monebo study (STROBE-compliant article). Medicine (Baltimore) 2016;95:e4098.
[22] Mărginean CO, Bănescu C, Duicu C, et al. Angiotensin-converting enzyme gene insertion/deletion polymorphism in nutritional disorders in children. Eur J Nutr 2015;54:1245–54.
[23] Mărginean C, Bănescu C, Duicu C, et al. The role of IL-6 572 C/G, 190 C/T, and 174 G/C gene polymorphisms in children's obesity. Eur J Pediatr 2014;173:1285–96.
[24] Mărginean CO, Mărginean C, Voidăzan S, et al. Correlations between leptin gene polymorphisms 223 a/g, 1019 g/a, 492 g/c, 976 c/a, and anthropometrical and biochemical parameters in children with obesity: a prospective case-control study in a romanian population-The Nutrichild Study. Medicine (Baltimore) 2016;95:e3115.
[25] Mărginean C, Mărginean CO, Iancu M, et al. The FTO rs9939609 and LEPR rs1137101 mothers-newborns gene polymorphisms and maternal fat mass index effects on anthropometric characteristics in newborns: a cross-sectional study on mothers-newborns gene polymorphisms-The FTO-LEPR Study (STROBE-compliant article). Medicine (Baltimore) 2016;95:e5551.
[26] Mărginean CO, Mărginean C, Melit LE. New insights regarding genetic aspects of childhood obesity: a minireview. Front Pediatr 2018;6:271.
[27] Mărginean C, Mărginean C, Iancu M, et al. The impact of TNF-α 308G>A gene polymorphism in child's overweight risk coupled with the assessment of biochemical parameters – a cross-sectional single center experience. Pediatr Neonatol 2019;60:19–27.
[28] Mărginean C, Bănescu CV, Mărginean CO, et al. Glutathione S-transferase (GSTM1, GSTT1) gene polymorphisms, maternal gestational weight gain, bioimpedance factors and their relationship with birth weight: a cross-sectional study in Romanian mothers and their newborns. Rom J Morphol Embryol 2017;58:1285–93.
[29] Mărginean CO, Melit LE, Chinceşan M, et al. Communication skills in pediatrics - the relationship between pediatrician and child. Medicine (Baltimore) 2017;96:e8399.
[30] Al-Samman M, Zuckerman MJ, Verghese A, et al. Gastric ulcers associated with herpes simplex esophagitis in a nonimmunocompromised patient. J Clin Gastroenterol 1994;18:160.
[31] Iriarte Rodríguez A, Frago Marquínez I, de Lima Piña GP. A case report: asymptomatic esophageal eosinophilia after herpes simplex esophagitis. Controversies in the therapeutic approach. Rev Esp Enferm Dig 2018;110:471–2.
[32] Bustamante KR, Burgos AG, Suárez CF. Eosinophilic esophagitis and herpetic esophagitis: cause or consequence? Rev Esp Enferm Dig 2017;109:393–4.
[33] Cronstedt JL, Bouchama A, Hainau B, et al. Spontaneous esophageal perforation in herpes simplex esophagitis. Am J Gastroenterol 1992;87:124–7.