Annals of Medicine and Surgery 84 (2022) 104839

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Case Report

Iron-deficiency anemia following herpetic esophagitis in a previously healthy female

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ARTICLE INFO

Keywords:
Case report
Herpes simplex virus
Esophagitis
Immunocompetence
Acyclovir
Anemia
Iron-deficiency
Gastrointestinal hemorrhage

ABSTRACT

Introduction: Herpetic Esophagitis is caused by the Herpes Simplex virus, which generally affects immunocompromised individuals and is rarely seen in healthy individuals. Symptoms are usually self-limiting.

Case presentation: We report the case of a 68-year-old female who presented with odynophagia, dysphagia, and epigastric pain with no other underlying disease. Endoscopic findings of soft, nodular, and friable growths just above the squamocolumnar junction with diffuse ulcerations in the distal esophagus, led to the diagnosis. It was confirmed with a histopathological report which revealed multinucleated giant cells with eosinophilic intranuclear inclusions. During follow-up, laboratory investigations revealed iron deficiency anemia, which was the consequence of GI bleeding.

Clinical discussion: Herpes Simplex virus esophagitis can occur in immunocompetent individuals and even it can cause food impaction and GI bleeding, which can lead to Iron deficiency anemia.

Conclusion: Hence, follow-up of patients is important for early diagnosis and intervention of any complications that may arise.

1. Introduction

Herpetic esophagitis is caused by the Herpes Simplex virus (HSV), which generally affects immunocompromised patients and is only rarely reported in immunocompetent individuals [1]. In an Immunocompetent individual, a history of alcohol use, corticosteroids, extensive burns, autoimmune disease, malnutrition have all been identified as predisposing factors for herpetic esophagitis [2].

The presentation of Herpetic Esophagitis varies from dysphagia, odynophagia, fever, chest pain, to respiratory symptoms like cough [3]. In immunocompetent adults, herpetic esophagitis is usually self-resolving with no complications associated with the disease. Antivirals, such as acyclovir, have been seen to reduce the length of illness and have a symptomatic response [4]. We present the case of an immunocompetent female with herpetic Simplex Virus Esophagitis which complicated to upper GI bleeding leading to Iron-deficiency Anemia. We hereby declare that this work has been prepared and edited in line with the SCARE 2020 guidelines [5].

2. Case Presentation

A 68-year-old female patient presented in the emergency department of Shree Birendra Hospital with complaints of five days of progressive odynophagia and dysphagia, for both liquids and solids. She also complained of nausea, anorexia, and epigastric pain. She was unable to tolerate oral intake. So, the patient self-medicated with omeprazole and antacids but this did not relieve. There was no history of weight loss. The patient had a smoking history (three packs a year) for approximately three years. Her past medical and surgical history is unremarkable. She had no past history of using immunosuppressive medications or steroids. There was no history of drug allergies or gastroesophageal reflux disease (GERD).

Her vitals were stable. On general examination, the patient was afebrile, non-cyanotic, and anicteric with no lymphadenopathy in her cervical, axillar, or inguinal regions. Her oral examination revealed no ulcers, blisters, or any discharge. There were no remarkable findings in her systemic examination.

Following her symptoms, initial baseline investigations were sent. The reports were normal. No remarkable findings were seen in the

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https://doi.org/10.1016/j.amsu.2022.104839
Received 8 August 2022; Received in revised form 2 October 2022; Accepted 30 October 2022
Available online 5 November 2022

ultrasound of the abdomen. The serology for Hepatitis B surface antigen (HBsAg), Human Immunodeficiency Virus (HIV) I and II, and antibody to Hepatitis C virus (anti- HCV) were nonreactive.

Upper Gastrointestinal Endoscopy (UGI) was scheduled which revealed soft, nodular, and friable growths just above squamocolumnar junction (SCJ) with diffuse ulcerations in the distal esophagus (Fig. 1). No abnormalities were detected in the stomach and the proximal duodenum. Multiple biopsies from the ulcerated areas of the distal esophagus were taken and sent for histopathological analysis.

Histopathological examination revealed a large area of ulcer with inflammatory exudate (Fig. 2). Numerous viral inclusions in the nucleus (Cowdry type A inclusion bodies) and cytoplasm of multinucleated squamous cells at the margin of the ulcer are present (Fig. 3). They had a thickened nuclear membrane and clear halo along with ground glass inclusions. The remaining tissue was lined by non-keratinized stratified squamous epithelium and columnar epithelium with apical mucin-producing cells. There was no evidence of dysplasia or malignancy.

Serology of HSV I/II was performed and titers for both IgG and IgM were above the normal range. The diagnosis of the case as Herpes Simplex Virus Esophagitis was made based on the clinical history, endoscopic report, and confirmation was made by histological biopsy. Acyclovir (800mg, five times a day for seven days) reduced her symptoms. She was then discharged and was maintained for follow-up.

However, owing to the third wave of COVID-19 disease, she missed her initial follow-up and arrived at the hospital after two months. At this time, she complained of a sticking sensation of food (food impaction), generalized fatigue, and weakness. She provided the history of black tarry stool for more than a week about one and half months ago.

So, laboratory investigation of blood and stool was sent. The blood investigation indicated she had anemia (Table 1). Then, her iron profile was sent, which revealed severe iron deficiency anemia (Table 2). She was managed symptomatically. Iron sucrose (200 mg in 250mL in normal saline) was administered intravenously. Iron supplementation was used (capsule of Ferrous Ascorbate & Folic Acid). Pantoprazole

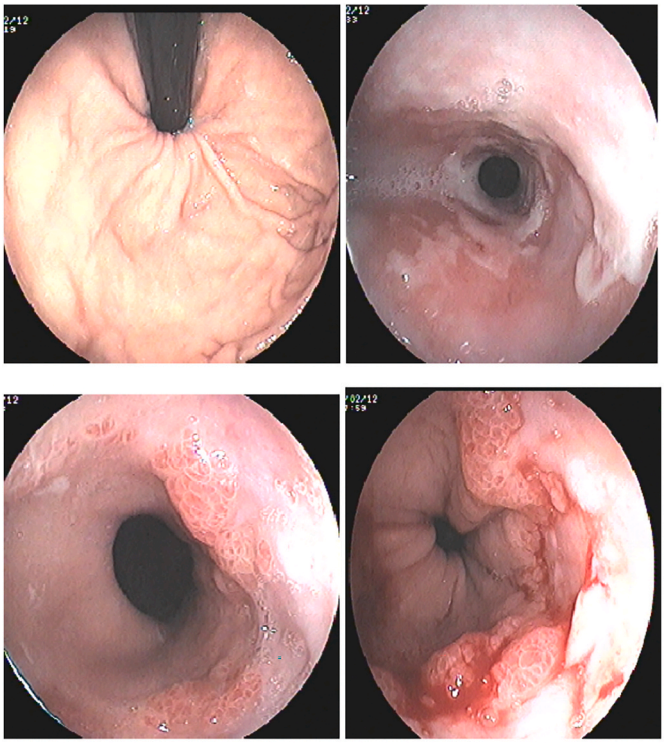

Fig. 1. Endoscopy of Herpes Simplex Virus Esophagitis on follow-up revealing soft, nodular, and friable growths noted just above SCJ with diffuse ulcerations in the distal esophagus.

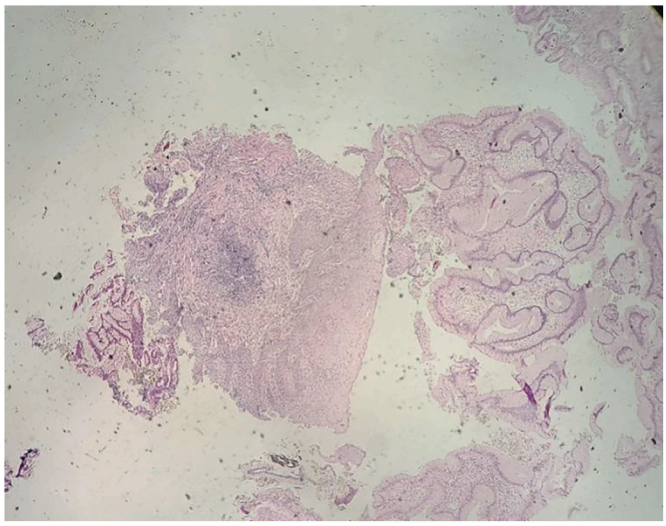

Fig. 2. Histology of Herpes esophagitis revealing areas of ulcer with multiple exudates.

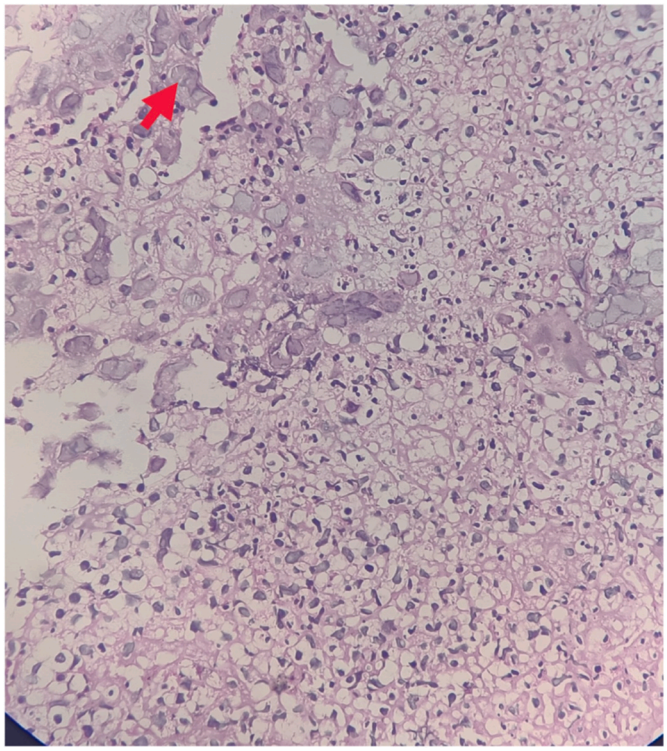

Fig. 3. Histological features of Herpes Simplex Esophagitis showing numerous viral inclusions in the nucleus (Cowdry Type A) and thickened nuclear membrane and clear halo along with ground glass inclusions.

tablet (40 mg, once daily) and vitamin C tablet (one tablet, once daily) were prescribed to the patient. At present, her symptoms have subsided.

3. Discussion

Esophagitis is most often caused by noninfectious conditions, such as gastroesophageal reflux disease, whereas esophageal infection occurs predominantly in those who have compromised immunity as a result of chemotherapy, transplantation, or HIV infection. Candida, Cytomegalovirus (CMV), and Herpes Simplex Virus (HSV) are the most common cause of infectious esophagitis [6]. Some incidences in

Table 1
Laboratory investigations during follow-up after 2 months.

Examination	Result
Hemoglobin	6.5 g/dL
Red Blood Cells	3.86 million/mm3
Total Leukocyte Count	4800 cells/cumm
Neutrophils	55%
Lymphocytes	36%
Monocytes	08%
Eosinophils	01%
Basophils	0%
Platelets	247,000 cells/cumm
Glucose (Random)	95 mg/dl
Urea	24mg/dl
Creatinine	0.7mg/dl
Sodium	146
Potassium	4.8
ALT	12UI/L
AST	36U/L
HIV1/II Ab test	Non-Reactive
HbsAg	Non-Reactive
HCV Ab test	Non-Reactive

Table 2
Iron profile of the patient during follow-up indicating iron deficinecy anemia.

Examination	Result (mcg/dL)
Serum Iron	67.66
Unsaturated Iron Binding Capacity (UIBC)	367.6
Total Iron Binding capacity (Iron + Unsaturated Iron)	435
Ferritin (Serum)	5.0

immunocompetent people have been reported [1,3,4,7–11]. The vast majority of infections are caused by HSV type 1 [7,8] although HSV type 2 has been occasionally reported.

The primary source of infection seems to vary depending on the patient's immune system's status. It is most likely due to local extension of the virus from an orolabial or pharyngeal source and subsequently, eroding the esophageal mucosa [12]. It is usually secondary to HSV reactivation in immunocompromised patients, with virus spread to the esophageal mucosa via vagus nerve or by direct extension of oral–pharyngeal infection into the esophagus [12]. The comprehensive review of previously reported cases by Canalejo et al. found that, in a cohort study of healthy adults and adolescents with herpes esophagitis, 11 of 25 evaluable cases had the original infection [6].

Patients usually present with odynophagia and dysphagia due to mucosal erosion and ulceration in the esophagus, based on previous cases and research [3,4,7–9]. Fever, epigastric pain [4,8], nausea, vomiting, cough, weight loss [8], and heartburn are less frequent [7]. Our patient presented a similar presentation of odynophagia and dysphagia. Nausea, anorexia, and epigastric pain were among our patient's complaints. Our patient, on the other hand, had neither chest pain nor fever. Occasional patients have coexistent herpes labialis or oropharyngeal ulcers but were absent in our patient.

Immunocompetency may affect the clinical presentation and complications. Extraesophageal lesions can be seen in some patients [6]. Complications and recurrence of Herpes esophagitis are uncommon, with just one case of the study by Galbraith et al. reporting it [10].

Most new infections remain undiagnosed and go untreated because they are asymptomatic or have only short-term symptoms [12] while in some cases, herpetic esophagitis may lead to bleeding [13,14], tracheoesophageal perforation [15], and food impaction [16]. In a few cases, intractable hiccups, eosinophilic esophagitis, weight loss [8] have been observed. During follow-up, our patient complained of food impaction. Severe Iron deficiency anemia was diagnosed. It was a challenge for us to determine whether the bleeding was caused by GI bleeding or by nutritional deficit due to anorexia. There was a history of anorexia but no weight loss in this time period. Although there was no active bleeding during the time of presentation, the patient had complained of black tarry stool (melena). Further investigations reveled no other sites of bleeding. Melena due to upper GI bleed from the ulceration of herpetic esophagitis in immunocompetent patients has also been observed in previous reports [13]. As a result, the finding strongly suggested that gastrointestinal bleeding was the cause of iron deficiency anemia. Hence, complications such as food impaction and GI bleeding might occur even in immunocompetent patients.

The advancement of diagnostic modalities and procedures in recent years has aided in obtaining an early diagnosis. Previously, herpetic esophagitis was only diagnosed in postmortem individuals [7]. Endoscopic findings are used to identify esophagitis and detect impacted regions of the esophagus. It is further confirmed by histopathological examination of the detected lesions. Upper Gastrointestinal Endoscopy (UGI) reveals soft, nodular, and friable growths [1] just above the squamocolumnar junction, as well as diffuse ulcerations in the distal esophagus [7,8,17]. The majority of patients have multiple esophageal ulcers. Ulcers are often small, discrete, coalescent, and superficial or punched out in appearance [7,8,17]. In most patients, the distal esophagus is the commonly involved region [7,8]. The endoscopic findings were similar in our patient, and the distal part was the affected part. Other pathologies that involve related endoscopic findings especially peptic esophagitis and cytomegalovirus esophagitis and immunological disorders, must be ruled out with further investigations [10].

Biopsies and brushings should be obtained from the ulcer margins, which are more likely to have viral cytopathic effects [18]. As a result, a biopsy was taken from the distal esophagus in our patient. Histologic findings include multinucleated giant cells, with ground-glass nuclei and eosinophilic inclusions (Cowdry type A inclusion bodies) occupying up to one-half of the nuclear volume, which are typical of Herpes Simplex virus infection [7]. The histopathological analysis of the biopsy of our patient revealed a large area of ulcer with inflammatory exudate. Numerous viral inclusions, in the nucleus (Cowdry type A inclusion bodies) and cytoplasm of multinucleated squamous cells at the margin of the ulcer, were present. The findings led to the conclusion of Herpes simplex infection, which was consistent with previously reported cases.

Serology helps in determining a recent or chronic infection. Furthermore, Immunohistopathology, HSV I/II serology and laboratory investigations should be performed to rule out any complications. Laboratory reports assisted us in identifying our patient's severe Iron-deficiency Anemia, which explained his symptoms of fatigue and generalized weakness. This is different from the conventional presentation. However, anemia has been reported in immunocompromised patient by Iida et al. [19]. Early detection enabled us to control the situation before it became severe.

Self-medication of omeprazole without success has been reported in earlier cases similar to ours by Marinho et al. Acyclovir is the preferred treatment of choice for herpetic esophagitis [1,10]. Although spontaneous resolution usually occurs in immunocompetent hosts in one to two weeks, patients with severe odynophagia may require hospitalization for antiviral therapy, pain management, and hydration or alimentation as anorexia can lead to nutritional deficiency, as well as to assess any complication present. Symptoms in our patient appeared to improve following a short course of acyclovir and she was discharged. However, an incidental finding of iron deficiency anemia was observed during follow-up. The patient was treated symptomatically.

Although the prevalence and incidence of complications in immunocompetent individuals are extremely rare, some patients may develop complications or a mild and subclinical nature of subsequent reactivation of HSV infection [1]. Hence, follow-up of patients is very important especially in immunocompromised patients as it leads to early diagnosis and assessment of any complications, as well as provision of symptomatic management timely.

4. Conclusion

Herpes simplex virus (HSV) infection of the esophagus is usually observed in immunocompromised individuals, although it can occur in immunocompetent individuals as well. In immunocompetent people, herpetic esophagitis is suspected clinically by the acute onset of odynophagia, dysphagia, and heartburn. Nausea, anorexia, epigastric pain may also be seen. It can result in GI bleeding issues and as a result, Iron deficiency anemia. Diagnosis is usually established with an upper endoscopy and confirmed by a biopsy of the lesion. Acyclovir is highly beneficial for a symptomatic response. Patients must be assessed timely and follow-up is very crucial. Otherwise, even in immunocompetent patients, complications like GI bleeding resulting in Iron deficiency Anemia may occur. Early intervention with symptomatic management is required for the complications if present.

Ethical approval

This is a case report, therefore, it did not require ethical approval from ethics committee.

Funding

The study did not receive any grant from funding agencies in the public, commercial or not-for-profit sectors.

Author contribution

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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AMB, RS, AK were involved in the conceptualization of the study, data collection, and writing case details. AMB, PR collected the data. AMB, PR were involved in the literature review and prepared the initial manuscript draft. AMB and KR prepared the final manuscript after revising and editing the initial draft. KR supervised the study.

Registration of research studies

Not applicable.

Guarantor

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Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-chief of this journal on request.

Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

The authors report no conflicts of interest.

Acknowledgement

We are grateful to Dr. Binod Karki (DM, Gastroenterology) for providing necessary case details, reviewing the article and providing valuable feedback.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104839.

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