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## Case and Review

# Rare Etiology of Odynophagia in a Female Adolescent

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## Keywords

Herpes esophagitis · Adolescent · Immunocompetent · Acyclovir

## Abstract

Herpes esophagitis (HE) is a rare condition in immunocompetent adolescents. However, it commonly occurs as a primary infection in younger individuals. Herein, we report a 16-year-old female patient who had a history of fever for 5 days, odynophagia, and orolabial herpes infection for 7 days. Clusters of painful vesicles on an erythematous base on the lips, gingiva, and palate were observed on physical examination. Further, esophagogastroduodenoscopy revealed diffuse linear ulcerations in the distal esophagus. The patient then received the following treatment: intravenous (I.V.) acyclovir 5 mg/kg three times a day, I.V. omeprazole 40 mg two times a day, and acyclovir 5% cream four times a day. After 8 days of admission, the patient was discharged. A follow-up esophagogastroduodenoscopy was performed 7 weeks after discharge, and the results revealed that the esophageal mucosa had a normal appearance. The effect of antiviral treatment against HE remains unknown in these patients. Nevertheless, it is believed to accelerate the healing process in individuals with esophageal mucosal barrier damage. To the best of our knowledge, this case of a female adolescent with an intact immune system is the sixth case of herpes simplex esophagitis to be reported in the literature.

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## Introduction

Herpes simplex viruses have a double-stranded DNA and are classified into two distinct types, which are as follows: herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2). They are transmitted after contact with infectious secretions that contain either HSV-1 (commonly detected in oral secretions) or HSV-2 (usually found in genital secretions). HSV-1 in the gastrointestinal tract frequently induces orofacial and esophageal herpetic lesions, and HSV-2 often causes perianal and rectal herpetic lesions [1]. The esophagus is commonly involved in patients with AIDS or an underlying malignancy, those receiving immunosuppressive therapy and, finally, terminally ill patients who underwent nasogastric intubation. Further, it is attributed usually to virus reactivation and rarely to primary infection [1].

The most common clinical features of herpes esophagitis (HE) are dysphagia, odynophagia, chest pain, and fever. Although the disease is usually self-limiting, severe complications, such as upper gastrointestinal hemorrhage and esophageal rupture, may be observed [1, 2]. On endoscopy, HE can appear as discrete or continuous ulcers with superficial or deep appearance with or without overlying exudates or, even rarely, as necrotic changes in the mucosa in the middle and distal esophagus [3].

Diagnosis is confirmed using at least one of the following methods: serology, histopathology, immunohistochemistry, HSV isolation from oropharyngeal secretions or esophageal tissue culture, and HSV genome detection via polymerase chain reaction (PCR) using esophageal biopsy specimens. The characteristic histological findings of HE are the presence of eosinophilic intranuclear inclusion bodies (Cowdry type A inclusion bodies) and/or multinucleated giant cells with ground-glass nuclei in epithelial cells on hematoxylin and eosin staining [4]. Treatment with intravenous acyclovir may resolve symptoms. Valacyclovir and famciclovir can also be used in patients who can take oral medications. However, data on their effect against HE are limited [4].

## Case Presentation

A 16-year-old female patient with a history of fever for 5 days, odynophagia, and orolabial herpes infection for 7 days visited the accident and emergency department. The patient had been previously treated with amoxicillin and famciclovir. Moreover, she had no significant surgical or medical history, including allergic disorders, gastroesophageal reflux disease, and eosinophilic esophagitis (EoE).

The patient was afebrile, anicteric, and slightly dehydrated. Physical examination revealed clusters of painful vesicles on an erythematous base on the lips, gingiva, and palate. However, the results of other clinical examinations were not remarkable. Esophagogastroduodenoscopy (EGD) was urgently performed, and results revealed diffuse linear ulcerations in the distal esophagus (Fig. 1). Multiple biopsy samples were collected from the edges of the ulcers. Results did not show the presence of tissue eosinophils. Moreover, the characteristic histopathologic features of HE, such as multinucleated cells with overlapping nuclei and ground-glass appearance, were not observed [3]. Based on an extensive initial workup, the

patient did not present with candidiasis or hematological disorders, immunodeficiency, and viral disorders including HIV infection.

IgM and IgG, which are specific antigens against HSV, were not detected using enzyme-linked immunosorbent assay. This phenomenon could be explained by the fact that our patient presented with a primary infection that was likely caused by local spread of the virus from the orolabial lesions. Thus, she was empirically treated with intravenous (I.V.) acyclovir 5 mg/kg three times a day, I.V. omeprazole 40 mg two times a day, and acyclovir 5% cream four times a day for concurrent orolabial herpes infection.

On day 2, the patient experienced significant clinical improvement and rapid recession of the orolabial lesions. On day 8, she was discharged from the hospital with the following take-home medications: oral acyclovir 400 mg three times a day and acyclovir 5% cream four times a day for another 6 days and oral omeprazole 40 mg two times a day for another 7 weeks. A follow-up EGD was performed 7 weeks after discharge, and results revealed that the esophageal mucosa had a normal appearance (Fig. 2).

## Discussion

HE is not common in immunocompetent adolescents. In this case, it was clinically suspected in a healthy individual who presented with odynophagia and a history of painful orolabial lesions for 7 days, which are indicative of orolabial herpes. Thus, an endoscopic evaluation was performed, and results showed severe erosive distal esophagitis. The patient received aggressive empirical antiviral treatment based on the endoscopic findings and the presence of concurrent herpes orolabial prior to confirmation via histological and serological examinations. In addition, our decision was based on the fact that there was no access to viral culture and PCR for the detection of HSV in oropharyngeal secretions or esophageal tissue specimens.

At present, the effect of antiviral treatment in immunocompetent patients is not fully elucidated due to the lack of comparative studies. Nevertheless, it should be considered based on symptoms and the severity of endoscopic findings to reduce recovery time and consequently prevent life-threatening complications such as upper gastrointestinal bleeding and esophageal perforation [5].

In addition, we searched MEDLINE to review relevant studies conducted in the literature from 1950 to 2019. The following keywords were used: “herpes simplex,” “esophagitis,” “immunocompetent,” “child,” and “adolescent.” We included all cases of HE, as defined by the World Health Organization, in immunocompetent adolescents aged between 10 and 19 years. In total, 36 cases were identified [4, 6–18]; the clinical characteristics of the patients are shown in Table 1. The mean age was  $15.097 \pm 2.736$  years, and the male: female ratio was 6.2:1. The most common manifestations were fever (69.44%), odynophagia (69.44%), and retrosternal pain (55.55%). Coexisting herpetic orolabial and skin lesions were observed in 11 (30.55%) cases. The most common endoscopic lesions were numerous ulcers (79.41%), whitish exudates (47.05%), and erythematous mucosa (35.29%). The most frequently affected sites were the distal (54.54%) and middle (45.45%) esophagus, and the whole

esophagus was involved in 12 (36.36%) patients. Diagnosis was made via histopathologic examination in 14 (33.33%) cases, and 9 (27.27%) patients had positive immunohistochemical staining results. HSV was identified via viral culture from esophageal brushing or using biopsy specimens in 26 (78.78%) and via serology (high IgM antibody titer or seroconversion) in 12 (36.36%) cases. In 5 of 36 (13.88%) patients, the diagnosis was made via HSV genome detection using PCR in esophageal biopsy samples. Although this method had a high sensitivity (94.7%) and a negative predictive value (96%), it is not widely available [20]. Finally, 23 (69.69%) patients received antiviral therapy with a mean symptoms-relief period of  $7.38 \pm 5.23$  days.

Three male patients with a mean age of 13.63 years had concomitant EoE and HE, and an 11-year-old boy presented with EoE after HE resolution. To date, whether HSV infection induces EoE or whether EoE is a risk factor for HE is not fully elucidated. The first theory proposed that HSV impairs the integrity of the esophageal mucosa barrier, thereby easing the passage of food antigens, which can trigger the Th<sub>2</sub> immune response. This mechanism in turn boosts esophageal eosinophilic mucosal inflammation [20]. The second theory shows that EoE precedes HSV infection, considering that the damaged esophageal mucosal is exposed to the virus [19]. In EoE, the widening of paracellular spaces, low levels of tight junction proteins, and presence of desmosomes with structural abnormalities are indicative of mucosal barrier loss [21].

Nevertheless, if HE is suspected in an adolescent, an extensive workup should be performed to rule out a coexisting primary or secondary immunodeficiency disorder (including HIV infection). Moreover, at least 10 biopsy samples should be collected from the edge of the ulcers for histologic evaluation and viral culture or PCR assays. A follow-up EGD should be performed within 8 weeks to rule out EoE.

### Statement of Ethics

A written informed consent for the publication of this case report and any accompanying figures was obtained from the patient's parents.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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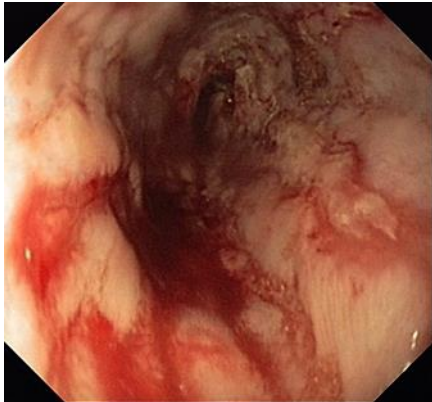
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## Author Contributions

A.K.: wrote the manuscript, performed literature search, made revisions, and submitted the manuscript. M.S., A.G., and M.F.: provided critical feedback on the manuscript.

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**Fig. 1.** Endoscopic appearance on admission.



**Fig. 2.** Endoscopic appearance in the fourth week after discharge.

**Table 1.** Clinical characteristics of HSV esophagitis in the immunocompetent adolescents

No.	Age	Sex	Symptoms	Endoscopic findings	Location	Other herpetic lesions	Diagnosis	Antiviral treatment	Days of resolution
1	10	M	F, RP	U, Ex	NR	No	C, S	No	5
2	12	M	F, V, He	U, Ex	D	Yes	C	Yes	1
3	10	M	F, RP, O	NR	NR	No	C, S	NR	NR
4	12	M	F, RP	NR	NR	Yes	C	NR	NR
5	19	M	F, O, BWL, URTI	U	D	Yes	C, S	No	17
6	18	M	O, Dy	U	Mi	No	H	No	NR
7	19	M	F, O	U	Mi	No	C	No	NR
8	14	M	F, RP, O, BWL, URTI	U, Ex	E	Yes	C	No	7
9	17	M	F, RP, O, BWL	U	Mi, D	No	C	No	5
10	17	M	O, BWL	U	D	No	C, S, IH	NR	18
11	19	F	F, RP, O	R, Ex	Mi, D	No	C, S, H, IH	Yes	17
12	19	M	F, O, Ep, URTI	U	P	Yes	C, S	Yes	4
13	14	M	F, O, V	U	Mi, D	No	C, H, IH	Yes	1
14	14	F	F, RP, Dy	R, Er	E	No	H	Yes	1
15	17	M	RP, Dy, V, URTI	U	Mi, D	Yes	C	Yes	10
16	11	M	F, RP, O, Dy	U, R	Mi, D	Yes	C, S, H, IH	Yes	10
17	14	M	F, RP, O, Ep, POI	U	D	No	C, S, H	Yes	10
18	17.6	M	RP, D	Er, Ex, R	D	No	C	Yes	NR
19	11.6	M	F, RP, D, V	U	Mi, D	No	C	Yes	NR
20	15.4	M	RP, O	Ex	E	No	C	Yes	NR
21	13.4	M	RP, O, BWL	U, Ex	E	No	C	Yes	NR
22	15.8	F	F, O	U, R, Er	E	No	C	Yes	NR
23	11.5	M	F, D, V	U, Ex	E	No	C	Yes	NR
24	16.2	M	RP, D, V	R, Er, Ex	E	No	C	Yes	NR
25	14	M	F, O	Ex	E	No	H, IH, PCR	Yes	NR
26	16	M	O, Dy	U	E	No	C, S	Yes	NR
27	13	M	F, O, Ep	Er	Mi, D	Yes	C, S, H	Yes	10
28	18	M	F, O, D, Ep, V	U, R, Ex	E	Yes	H, IH	Yes	14
29	17	F	RP, Ep, He	U, R	Mi, D	No	S, H, IH, PCR	No	NR
30	16	M	F, RP, O	U	Mi, D	No	C, H	Yes	5
31	13	M	F, RP, O	U, R, Ex	E	No	C, S, IH	No	NR
32	12	M	F, RP, O	U, R	E	Yes	S	Yes	NR
33	17	M	F, RP, O	U, R, Ex	Mi, D	No	PCR	No	NR
34	16	M	F, O, Dy	U, R, Ex	Mi, D	No	PCR	No	NR
35	19	F	Dy	U, Ex	Mi, D	No	H, IH	Yes	10
36	15	M	O	U, Ex	Mi, D	Yes	PCR	Yes	3

BWL, body weight loss; C, culture; D, distal esophagus; Dy, dysphagia; E, entire esophagus; Ep, epigastric pain; Er, erosions; Ex, exudates; F, fever; H, histology; He, hematemesis; IH, immunohistochemistry; Mi, mid-esophagus; NR, not reported; O, odynophagia; P, proximal esophagus; PCR, polymerase chain reaction; POI, poor oral intake; R, redness of esophageal mucosa; RP, retrosternal pain; S, serology; U, ulcers; URTI, upper respiratory tract infection; V, vomiting.