

## Case Report

# Intractable hiccups due to herpetic esophagitis in an immunocompromised patient



John Harris<sup>\*</sup>, Tukisa Smith, Jana Preis

SUNY/Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203, United States

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## ABSTRACT

*Introduction:* Herpes virus family's association with visceral lesions is well established. Herpes simplex virus presentations vary based on immune status. Intractable hiccups due to herpes simplex esophagitis, to the best of our knowledge have been described twice in the literature. We present a 68 year-old immunocompromised male with intractable hiccups for 10 months.

*Case:* 68 year-old male with end-stage renal disease and multiple myeloma presented with coffee ground emesis and hiccups of ten months duration. A year earlier, he received cycles of bortezomib and dexamethasone, remaining on lenalidomide. During chemotherapy, he developed pneumococcal meningitis and subsequently intractable hiccups. Preceding admission, endoscopy showed duodenitis and esophagitis. Proton-pump inhibitor therapy was initiated; however, biopsy was not performed.

During admission, hiccups often occurred every few seconds while off anti-emetics, persisting despite therapy. Exam showed cachexia/temporal wasting, aphthous stomatitis and abdominal tenderness. MRI of brain/spine, CT of neck, chest, abdomen and neurological evaluation were unremarkable. Endoscopy revealed gastritis and esophagitis with mucosal tears. Biopsy revealed intra-nuclear inclusions with multi-nucleated cells, consistent with herpes virus, later confirmed as herpes simplex by immunostaining. Hiccups and emesis resolved after of 2 days of intravenous acyclovir. 21 days of treatment were completed with oral valacyclovir. He remained free of hiccups during the remaining hospital stay and follow up.

This case illustrates an exceptionally rare presentation of herpetic esophagitis in an immunocompromised host. As novel immunotherapeutic/suppressive agents continue to emerge, the evolving role of herpes virus prophylaxis and diagnosis of atypical presentations in new host populations is a topic of growing importance.

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The first association of a member of the Herpes virus family and visceral lesions was established in 1940 by Johnson [1]. Since then, Herpes simplex virus (HSV) has played a well defined role as the etiologic agent in infectious processes throughout the GI tract, in the immunocompromised, as well as immunocompetent host. Within the GI tract, HSV-1 is most commonly associated with oral and esophageal herpetic lesions, while HSV-2 is more commonly associated with proctitis, most notably in the homosexual male population. In a 2003 autopsy series of 1307 cases, the reported incidence of herpetic esophagitis was 1.8%. Of the 24 cases of herpes simplex esophagitis (HSE) identified, 18/23 (75%) were associated with underlying malignancy some of whom received

chemotherapy, while the remaining 5/23 (21%) cases were associated with underlying immunocompromise or a condition requiring immunosuppressive therapy. In many of these cases, documented clinical symptoms of esophagitis were absent [2]. Among the immunocompromised population, HSV was most commonly associated with esophagitis in bone marrow transplant recipients not on antiviral prophylaxis. In a study of esophageal infections in patients after bone marrow transplantation, HSV was implicated as a sole pathogen or co-pathogen in 10/17 (58%) cases of patients with findings on endoscopy [4]. In another study of 221 renal transplant patients, the diagnosis of HSV esophagitis was made in 5 (2.2%) patients [5]. In the AIDs population, many of the studies of herpetic esophagitis (HE) were carried out prior to the introduction of effective anti-retroviral therapy (ART) and in one prospective study of AIDs patients not on ART, HE occurred in 4 of 145 patients (2.5%) [6]. Although HSE is much more common in the

<sup>\*</sup> Corresponding author. Tel.: +1 7705619205.  
E-mail address: [willistonharris@gmail.com](mailto:willistonharris@gmail.com) (J. Harris).

immunocompromised, rarely it occurs in the immunocompetent individual, most often representing primary infection. In a study of immunocompetent individuals, the most common presenting symptoms included acute odynophagia (76.3%), heartburn (50%) and fever (44.7%) [3]. Intractable hiccups (singultus) due to herpes simplex esophagitis, to the best of our knowledge has only been described on 2 other occasions in the literature to date. Here we present the case of a 68 y/o immunocompromised male who presented with intractable hiccups for 10 months.

### Case report

A 68 year old African American male with a history of hypertension, end-stage renal disease and multiple myeloma presented to the emergency department for evaluation of recurrent coffee ground emesis associated with chronic hiccups of ten months duration. The year prior, he was diagnosed with multiple myeloma, completing nine cycles of bortezomib and dexamethasone with poor response. Additional chemotherapy with lenalidomide was initiated and continued until admission. Ten months prior to admission, his chemotherapy was interrupted due to an episode of pneumococcal meningitis after which he developed intractable hiccups. He had multiple evaluations for hematemesis, requiring several blood transfusions in the four months prior to admission. Endoscopic findings were significant for duodenitis, esophagitis and he was treated with proton-pump inhibitor therapy. However, a biopsy had never been performed.

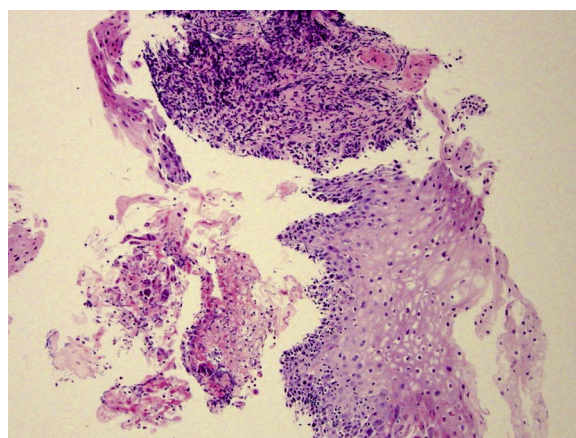
During admission, hiccups occurred as often as every 2–3 s while off chlorpromazine or ondansetron. In addition to hematemesis present on admission, he reported chronic abdominal pain secondary to hiccups but notably absent were signs of dysphagia or odynophagia. Review of systems was significant for fatigue, nausea, anorexia and weight loss. Physical exam was significant for cachexia, temporal wasting, aphthous stomatitis involving the tongue and diffuse abdominal tenderness. Initial laboratory studies were significant for low hemoglobin (8.3 g/dL) and an elevated BUN/Cr (16/3.8 mg/dL), consistent with end stage renal disease. Initial imaging on admission included a chest X-ray which was unremarkable. Throughout admission, his hiccups persisted despite maximum dosing of ondansetron and chlorpromazine, although with moderate improvement. Even as an outpatient, during the prior ten months of oral chlorpromazine therapy his hiccups never completely resolved. Inpatient neurological evaluation and extensive imaging which included MRI of the brain/spine, CT of soft tissue of the neck and CT of the chest and abdomen failed to reveal any central process or obvious organic cause of vagus or phrenic nerve irritation.

Given the persistent hematemesis despite proton pump therapy, endoscopic evaluation was performed. In comparison to endoscopic evaluation one week prior, which showed mild duodenitis and severe diffuse esophagitis with shallow ulcerations in a circumferential fashion at the gastro-esophageal (GE) junction, repeat endoscopic findings included mild gastritis with persistent duodenitis and severe diffuse esophagitis now with mucosal tears. During this study, no biopsies were obtained secondary to esophageal friability. Given the mucosal appearance, there were initial concerns for eosinophilic esophagitis in which presumptive treatment with corticosteroids were considered, however, only symptomatic management was decided until repeat endoscopic evaluation with biopsy could be performed (Images A–F).

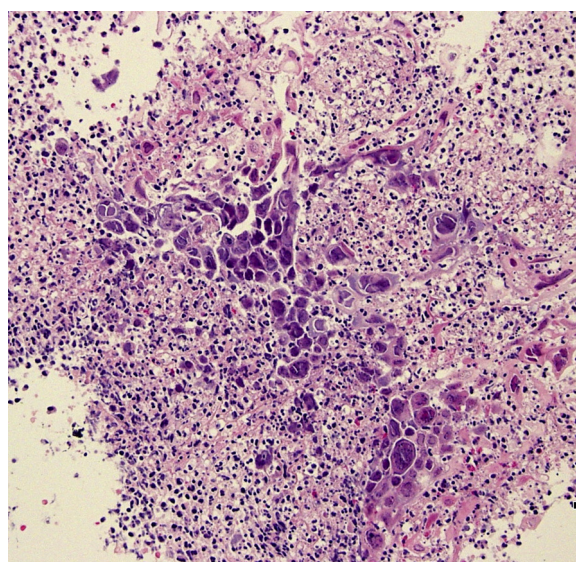
Five days later repeat endoscopic evaluation with biopsies from the middle and distal esophagus were performed. Pathology was notable for numerous intranuclear inclusions with multinucleated cells (see below) consistent with a viral process. Specific immunostaining confirmed the presence of herpes simplex virus (not specific to type). Evaluation for concurrent HIV infection was



**Image A.** Endoscopic view: two shallow, friable linear ulcerations extending to the gastro-esophageal junction, otherwise normal appearing mucosa.

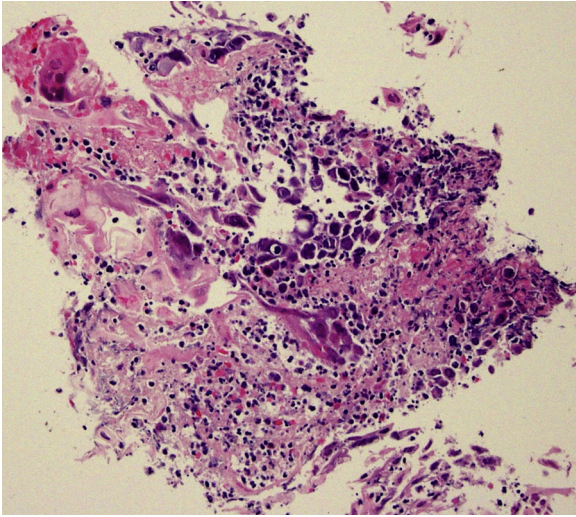


**Image B.** (above): Esophageal mucosa with chronic inflammation and adjacent necrotic tissue 100 $\times$ .

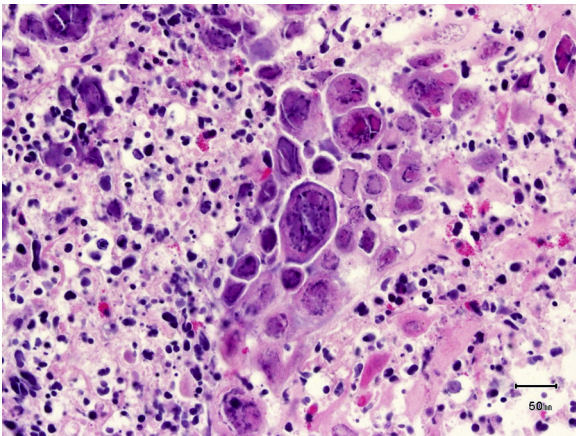


**Image C.** (above): Necrotic tissue with intranuclear inclusion-bearing cells 200 $\times$ .

negative by enzyme-linked immunosorbent assay (ELISA). Neither cytomegalovirus polymerase chain reaction (PCR) nor IgM were performed, although IgG was positive, indicating carrier status. Intravenous acyclovir was promptly initiated in addition to



**Image D.** (above): Necrotic tissue with intranuclear inclusion-bearing cells 200×.



**Image E.** Characteristic Herpes simplex intranuclear inclusions. Some cells are multinucleated 400×.

standing orders of intramuscular chlorpromazine and intravenous ondansetron. Within two days, the patient reported complete resolution of singultus and emesis. Given the patient's response with the addition of acyclovir, he no longer required anti-emetics or chlorpromazine and completed a successful trial of oral intake so after. After completing 5 days of intravenous acyclovir, he was transitioned to oral valacyclovir, thus completing a 21-day course of treatment as outpatient. Throughout the remaining hospital course and brief outpatient follow up, he remained free of hiccups and intractable vomiting. Unfortunately, long term follow up was not possible as he expired soon after discharge, likely related to his underlying malignancy.

## Discussion

Herpes simplex virus is a member of the Herpesviridae family, which contains linear, double stranded DNA surrounded by an outer glycoprotein layer [7]. Although HSV-1 and HSV-2 are genetically 70% homologous, HSV-1 has a greater propensity for oral and GI infections. Although HSV as a cause of esophagitis has been well described, this unique presentation of intractable hiccups as in our case is exceedingly rare. Of the two cases described in the literature, one an immunocompromised individual with renal allograft rejection and the other, an immunocompetent



**Image F.** Aphthous ulcers on tongue.

individual, who underwent thoracotomy and coronary bypass [8,9]. Similar to our case, dysphagia and odynophagia were notably absent in the case of the immunocompromised individual described in the literature. However in our case, a noteworthy difference was the duration of the hiccups, which were consistently present for several months prior to presentation. Many causes of intractable or persistent hiccups have been described in the literature. Among those included are various metabolic, gastrointestinal, central nervous system, thoracic and cardiovascular disorders. Irritation of the vagus and phrenic nerve, malignancy, adverse drug reactions and psychogenic causes has all been implicated [10,11]. Our patient received extensive work up, including neuro-imaging and no other obvious etiology of the hiccups was identified.

In immunocompromised populations, the predisposition of HSV reactivation is in part related to deficient cell mediated immunity, which is thought to play a more important role than humoral immunity in prevention of reactivation of herpes virus. However, since multiple myeloma is characterized by deficient humoral immunity, the increased risk of herpes virus infections in this population is largely a result of the treatment modalities and not the disease itself [12,13]. In the recent 2005 study, the APEX trial, bortezomib vs. high dose dexamethasone therapy alone for patients with relapsed multiple myeloma was associated with a statistically significant higher incidence, 13 vs. 5% of Herpes zoster infections [14]. While some authors believe bortezomib therapy is linked to an increased propensity of HSV reactivation, the evidence is less clear [12]. In a 2012 study, patients given prophylactic acyclovir showed a significantly lower incidence of varicella zoster virus (VZV)/complicated HSV while on lenalidomide based protocols for multiple myeloma [13]. Antiviral prophylaxis with acyclovir has since been recommended in these patients. However, our patient did not receive it.

On endoscopic examination, the most frequently affected site is the distal esophagus, with extensive esophageal involvement often occurring. Typical findings include inflamed mucosa, often friable with occasional hemorrhagic changes. Ulcerations are often numerous and may be superficial or "punched out," often arranged in a linear fashion and containing whitish exudates [3]. In a small review of 38 cases of immunocompetent individuals with HSE, microscopic findings consistent with acute and chronic inflammation were present, along with cytopathologic changes and viral inclusion bodies consistent with herpetic infection were present 68.4% of the time [3]. These non-specific histologic findings which include ballooning degeneration of epithelial cells, multinucleated giant cells and cowdry type A inclusion bodies can also be found in other herpes virus infections and are not limited to HSV. In the

same review, the best method of diagnosis was virus isolation from biopsied esophageal tissue which was positive (95.8%) of the time, followed by immunocytochemistry (87.5%) and histopathology (68.4%) as previously mentioned [3]. Detection of HSV DNA by PCR may also be used to improve diagnostic yield in selected cases [16].

Treatment of herpetic esophagitis is rarely required in immunocompetent individuals. The course is self limited, usually resolving within a week. Data showing benefit from treatment in this group is lacking [3,15]. In the immunocompromised host, older data regarding treatment of HSV esophagitis has come from mostly small case studies of bone marrow and solid organ transplant recipients, in whom acyclovir prophylaxis is now routinely indicated [4,5,19]. Data from larger more recent studies has been from AIDs patients. In a study of 34 AIDs patients with confirmed or probable HSV esophagitis treated with acyclovir, complete clinical responses were achieved in 24 (71%) patients within a mean of 9 days of treatment and resolution of ulcerations was endoscopically confirmed for 12 patients. Partial responses occurred in 3 (9%), with a remaining 6 (18%) lost to follow up and 1 treatment failure [18]. In general, treatment is recommended in the immunocompromised, while prophylaxis is recommended in certain heavily immunosuppressed subgroups, as these populations are at greater risk for disseminated herpes virus infections and worse outcomes [17,18]. In the case of our patient, although it may be difficult to establish direct causality, the fact that our patient promptly responded to anti-viral therapy with complete resolution of hiccups in 2 days makes a compelling argument as to HSV being the etiologic agent responsible. This prompt response to therapy was similar to past cases described in the literature.

## References

- [1] Johnson HN. Visceral lesions associated with varicella. *Arch Pathol* 1940;30:292.
- [2] Tohru I, Takahashi T, Kusaka K, Kawaura K. Herpes simplex esophagitis from 1307 autopsy cases. *J Gastroenterol Hepatol* 2003;18:1407–11.
- [3] Ramanathan J, Rammouni M, Baran J, Khatib R. Herpes simplex virus esophagitis in the immunocompetent host: an overview. *Am J Gastroenterol* 2000;95:2171–6.
- [4] McDonald G, Sharma P, Hackman R. Esophageal infections in immunosuppressed patients after marrow transplantation. *Gastroenterology* 1985;88:1111–7.
- [5] Mosimann F, Cuenoud P, Steinhauslin F, Wauters J. Herpes simplex esophagitis after renal transplantation. *Transplant Int* 1994;7(2):79–82.
- [6] Connolly GM, Hawkins D, Harcourt JN, Parsons PA. Oesophageal symptoms, their causes, treatment and prognosis in patients with the acquired immunodeficiency syndrome. *Gut* 1989;30:1033–9.
- [7] Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes virus; herpes simplex and varicella-zoster. *Lancet* 2007;6:1015–28.
- [8] Cain J, William A. Herpetic Esophagitis causing tractable hiccups. *Ann Int Med* 1993;119(3):249.
- [9] Mulhall B, Nelson B, Rogers L, Wong R. Herpetic esophagitis and intractable hiccups (singultus) in an immunocompetent patient. *Gastrointest Endosc* 2003;57(6):796–7.
- [10] Rizzo C, Caroline V, Montagnini M. Management of intractable Hiccups: an illustrative Case and Review. *AM J Hosp Palliat Care* 2014;31:220.
- [11] Marinella MA. Diagnosis and management of hiccups in the patient with advanced cancer. *J Support Oncol* 2009;7(4):122–7. 130.
- [12] Mauricio N, Elias A. Infection in patient with multiple myeloma in the era of high dose therapy and novel agents. *Clin Infect Dis* 2009;49(8):1211–25.
- [13] König C, Kleber M, Reinhardt H, Knop S, Wasch R, Engelhardt M. Incidence, risk factor, and implemented prophylaxis of varicella zoster virus infection, including complicated varicella zoster virus and herpes simplex virus infections, in lenalidomide-treated multiple myeloma patients. *Ann Hematol* 2014;93:479–84.
- [14] Richardson P, Schlossman R, Munshi N. Bortezomib or high dose dexamethasone for relapsed multiple myeloma. *N Eng J Med* 2005;352:2487–98.
- [15] Lavery E, Coyle W. Herpes simplex virus and the alimentary tract. *Curr Gastroenterol Rep* 2008;10:417–23.
- [16] Canalejo E, Duran FG, Cabello N, Martinez JG. Herpes Esophagitis in Healthy Adults and Adolescents, report of 3 cases and review of the literature. *Medicine* 2010;89:204–10.
- [17] Wilcox CM, Karowe MW. Esophageal infections: etiology, diagnosis, and management. *Gastroenterologist* 1994;2(September (3)):188–206.
- [18] Genereau T, Lortholary O, Bouchard O, Flore L. Herpes Simplex Esophagitis in patients with AIDS: Report of 34 Cases. *CID* 1996;22:926–31.
- [19] Kadakia SC, Oliver GA, Peura DA. Acyclovir in endoscopically presumed viral esophagitis. *Gastrointest Endosc* 1987;33:33–5.