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Case Report

Intractable hiccups due to herpetic esophagitis in an immunocompromised patient

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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.

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

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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 hematemsis 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 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

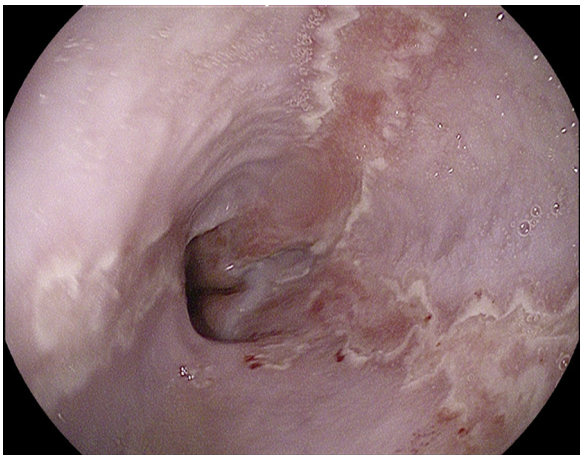

Image A. Endoscopic view: two shallow, friable linear ulcerations extending to the gastro-esophageal junction, otherwise normal appearing mucosa.

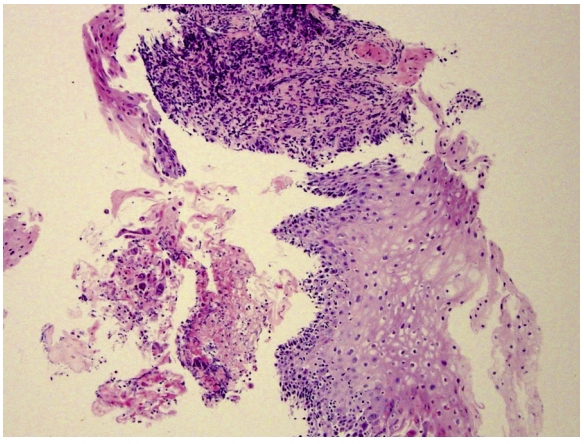

Image B. (above): Esophageal mucosa with chronic inflammation and adjacent necrotic tissue 100×.

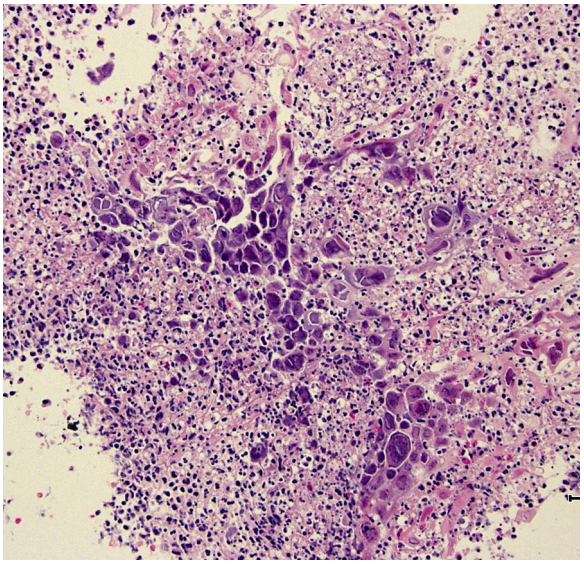

Image C. (above): Necrotic tissue with intranuclear inclusion-bearing cells 200×.