Head and Neck Pathol (2015) 9:119–122
DOI 10.1007/s12105-013-0516-2

CASE REPORT

Acute Necrotizing Herpetic Tonsillitis: A Report of Two Cases

Walaa M. Borhan · Mohammed A. Dababo · Lester D. R. Thompson · M. Saleem · N. Pashley

Received: 6 October 2013 / Accepted: 6 December 2013 / Published online: 14 December 2013

Abstract The finding of herpetic tonsillitis is rare. Tonsillectomies are usually done for children with recurrent chronic tonsillitis, while viral throat infections are generally self-limiting. We present two cases: A 5 year-old girl, with atypical hemolytic anemia managed with Eculizumab, who presented with a pharyngeal infection and tonsillar enlargement that did not respond to intravenous antibiotics or antifungal therapies; and a 30 year-old man who presented with upper airway obstruction and fever; bilateral tonsillectomies were performed. Histopathological examination showed a necrotizing tonsillitis with numerous ground-glass intranuclear inclusions, characteristic of herpes viral infection, further confirmed by Herpes simplex virus in situ hybridization. Both patients were managed by intravenous Acyclovir, with dramatic improvement.

Keywords Herpes simplex virus type-1 · Herpetic tonsillitis · Herpetic gingivostomatitis

W. M. Borhan (✉) · M. A. Dababo
Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
e-mail: dr.burhan@hotmail.com

L. D. R. Thompson
Department of Pathology, Southern California Permanente Medical Group, Woodland Hills, CA, USA

M. Saleem · N. Pashley
Department of Otolaryngology/Head and Neck Surgery and Communication Diseases, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Introduction

Acute sore throat is one of the most common reasons to visit a family practice physician. According to one study there are 200 visits per 1,000 population annually for this reason [1]. Symptomatic relief is the mainstay of treatment. The debate and controversy regarding antibiotic treatment has been going on for years with a variety of criteria that define its use.

The upper aerodigestive tract, including the oral cavity and oropharynx, are commonly affected by a host of different viral infections. Viral causes of tonsillitis include Epstein–Barr virus, parainfluenza, measles, Coxsackievirus, and adenovirus, among others. Herpes simplex virus type 1 can cause primary or recurrent infections, with the most common manifestation as acute gingivostomatitis in young children. The disease can extend into adjacent areas, such as the hard palate and tonsils. In adults, primary infection can result in acute pharyngotonsillitis. Reactivation of the herpes virus by any of several pathways (trauma, infection, change in immune status, environmental factors, etc.) may result in herpes labialis. In most cases the diagnosis is made clinically, and in some instances confirmation by laboratory tests is needed. However, acute, necrotizing herpetic tonsillitis is rare.

Case Reports

A 5 year-old girl presented to the emergency department, with a 3 day history of intermittent fever, dysphagia, gradual swelling of her cheeks and painful ulceration of the lips. Her past medical history was significant for membranoproliferative glomerulonephritis which was secondary to familial atypical hemolytic uremic syndrome

(aHUS) in addition to secondary hypertension due to her renal disease (managed by labetalol and furosemide). She also suffers from asthma, although medically managed by fluticasone and albuterol. She received injections of Eculizumab every 2 weeks for the past 10 months for her aHUS (a rare genetic disease associated with abnormal blood clotting, leading to small vessel damage, including kidney failure). Physical exam revealed right-sided diffuse neck swelling, drooling, and ulceration of the lower lip and buccal mucosa. Oral exam disclosed bilateral, grade 3 tonsillar enlargement with marked exudate. There was no trismus. Cervical lymphadenopathy could not be assessed due to neck swelling. The remaining physical exam was unremarkable. A complete blood count and differential was normal, while throat, nasopharyngeal, blood and urine cultures were negative. A monospot test was negative. Viral screening was negative for cytomegalovirus, Ebstein Bar virus and H1N1 and a multiplex PCR analysis for respiratory viruses was negative. A computed tomography scan with contrast showed bilateral heterogeneous contrast enhancement of the enlargement of palatine tonsils along with multiple enlarged bilateral cervical lymph nodes. No peritonsillar or neck space abscess was detected. She failed initial antibiotic therapy, and so vancomycin was started at the recommendation of the pediatric infectious disease specialist. Dysphagia accompanied airway obstruction, neck swelling and fever spikes to 39 °C over the subsequent 72 h. Emergency bilateral tonsillectomy was undertaken along with buccal mucosal biopsies. Oropharyngeal edema was significant, and so the patient remained intubated for 48 h in the pediatric intensive care unit, followed by an uneventful extubation.

The second patient was a 30 year old man with a sore throat, a low grade fever, headache and sense of malaise. His past medical history was unremarkable, except for a history of "core sores" on the lower lip, often triggered by extreme cold weather or sun exposure. He first noted the clusters of blisters on his neck and shoulders during college when he was a wrestler. However, the blisters only seemed to recur years apart, usually related to sun exposure or some kind of contact sport or trauma. Physical exam demonstrated remarkably enlarged tonsils bilaterally with a yellow exudate on the surface. No oral or lip lesions, nor other skin lesions were noted. Bilateral tonsillectomy and adenoidectomy was performed.

In both patients, the tonsils were enlarged (up to 4.5 cm), convoluted and cerebriform, covered by a yellow exudate. Serial sections at close intervals shows multifocal, soft, pus-filled pockets to granular areas of necrosis. Microscopically, the tonsils showed well developed lymphoid follicular hyperplasia in addition to areas of necrotizing granulomatous inflammation. The necrosis was primarily at the surface crypt epithelium, but expanded into the interfollicular zones of the tonsillar lymphoid tissue (Fig. 1a). Within the necrotic debris and immediately associated with the epithelium, multinucleated giant cells were noted. These giant cells show a thickened nuclear membrane, chromatin margination and a homogenous "ground glass" opaque basophilic to eosinophilic intranuclear inclusion (Fig. 1b), characteristic for a herpes virus infection. In one case an in situ hybridization was performed (Fig. 2) and in the second case an immunohistochemistry antibody for HSV1 (Novus Biologicals, Littleton, CO) was performed (Fig. 3), with both showing a strong nuclear reaction. These ancillary studies helped to confirm the diagnosis of herpes tonsillitis.

Both patients were given acyclovir, although the 5 year old girl required a 2 week course of intravenous treatment, while the 30 year old man took 800 mg orally five times a day for 5 days. Both patients fully recovered without complications.

Discussion

Upper respiratory tract infections are the commonest infections seen in both pediatric and adult populations, with

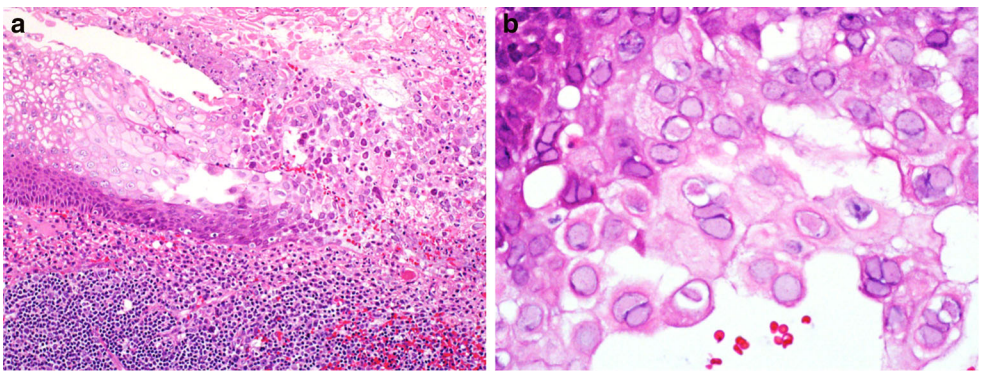

Fig. 1 **a** At low magnification, the necrosis and epithelial ulceration is seen in a background of lymphoid follicular hyperplasia. **b** A high power view of cells showing glassy intranuclear herpes simplex inclusion bodies

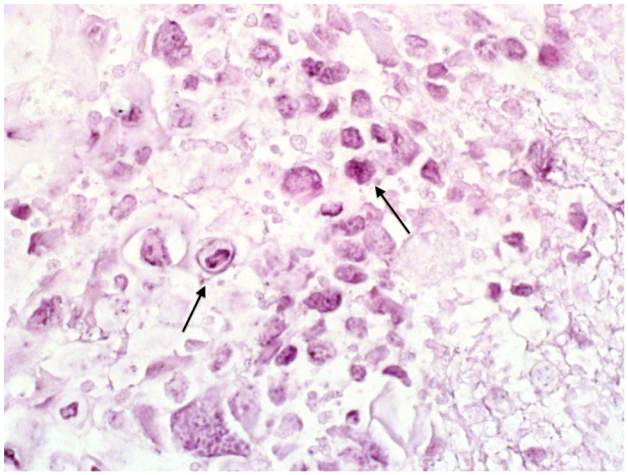

Fig. 2 In situ hybridization for HSV1 highlight the infected cell (*arrow*)

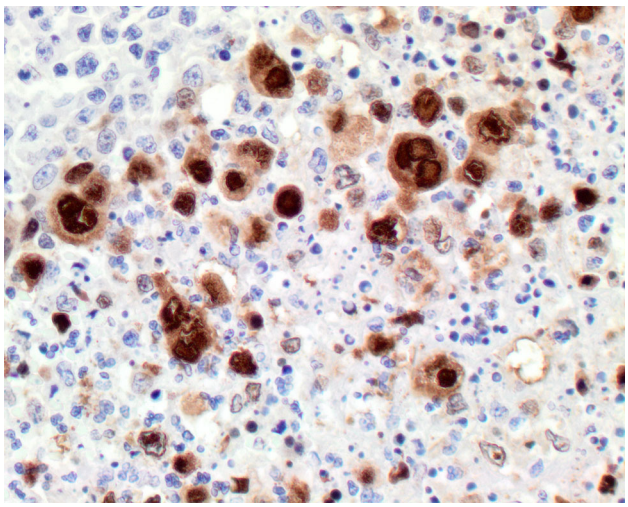

Fig. 3 Immunohistochemistry for HSV1 highlight the intranuclear viral inclusions

the majority caused by viruses, such as adenovirus, Epstein–Barr virus, parainfluenza, influenza A, coxsackie A, respiratory syncytial virus, and herpes simplex, among others [2]. Nearly all of these viral infections are of short duration and require only symptomatic management. In selected instances, especially in patients with an underlying immune deficiency, these types of infections can progress clinically to become fulminant infections associated with severe complication and even death.

Herpes simplex virus is an encapsulated double-strand DNA virus, which can cause an acute infection characterized by heavy viral shedding which may then be followed by a latent infection with periodic reactivation and recurrence at or near the initial primary site. The majority of oral herpetic infections are caused by herpes virus type 1 (HSV1), while genital infections are most frequently caused by HSV type 2 [3]. In general, infection by the virus results in immunity, preventing reinfection by the same virus.

HSV1 spreads via infected saliva or direct contact and typically occurs in young children. Oral lesions are usually symptomatic, presenting as a vesicle or blister (cold sore or fever blister) about 710 days after initial exposure (incubation period). The blisters are usually closely grouped (crops), affecting the mucosal lip (within the vermillion border) or gingiva [4], although the palate and tongue may also be affected. Systemic symptoms may include fever, lymphadenopathy, anorexia and irritability. Latent virus remains dormant in the sensory nerves and/or ganglia, resulting in periodic reactivation and recurrent infections at the mucocutaneous junction, especially of lips (thus, herpes labialis). Persistent following primary infections have been identified in numbers of anatomic site such as pharyngeal tissue, skin, cartilage and bone. [5]. Recurrent HSV1 infection within the mouth is uncommon in otherwise healthy patients [6]. Factors that activate the latent virus are diverse and encompass trauma, other respiratory tract infections, allergies, cold, sun exposure, stress, among others. In immunocompromised or immunosuppressed patients, this infection can result in a serious and sometimes fatal illness, often clinically unsuspected, requiring ancillary laboratory studies for diagnosis and confirmation.

Herpetic tonsillitis is usually self-limited, possibly associated with adenoid/tonsillar hypertrophy and chronic adenoiditis/tonsillitis, although results are different depending on ISH [7] versus PCR techniques [8]. There are only a few single case reports in the literature describing the histologic findings [9–15]. Patients reported are typically adults, as HSV1 tonsillitis is not in the clinical differential diagnosis for tonsillitis, as it may be for a child or in an immunocompromised patient [9, 11]. During a 10 consecutive year period, within a population of approximately 3,221,390 patients (mid-year patient count, 10 year average), 28,136 tonsillectomies and/or adenoidectomies were performed, yielding 87 tonsillectomies per 100,000 population per year (Southern California Permanente Medical Group incidence). Only a single case of HSV tonsillitis was identified during this 10 year period. This number is partially limited by a "gross only" examination protocol for tonsillectomies/adenoidectomies in patients <16 years of age, although if there are unusual findings clinically or macroscopically, histologic sections are submitted. Suffice it to say, acute HSV tonsillitis is rare.

The intra- and inter-cellular edema (acantholysis) results in nuclear enlargement with basophilic or eosinophilic nuclear inclusions surrounded by a clear halo (Fig. 1a, b). Cells may fuse to form giant cells. While standard hematoxylin and eosin stained slides show the characteristic viral inclusions within the infected cells, other techniques

help to confirm the diagnosis and exclude other viruses, such as Epstein–Barr virus (EBV) and cytomegalovirus (CMV). Immunohistochemical (IHC) reactions or in situ hybridization (ISH) can highlight the infected cells. IHC reactions may be limited by low antigen expression, but they are usually easier to prepare and interpret than ISH [11, 13]. In our cases, one patient was confirmed by ISH (Fig. 2) with the other confirmed by IHC (Fig. 3). Polymerase chain reaction (PCR) can also be employed in diagnosis. Viral culture and identification of HSV has been accepted as the *gold standard* for the laboratory diagnosis of HSV infection, but in a recent study by Espy et al. [16] use of PCR in the routine clinical laboratory provided a system that achieved a 22 % increase in sensitivity compared with shell vial cell culture, and was obtained in a shorter time [11]. Multiplex PCR assay has been used to show tonsils may be a reservoir for HSV1, playing a role in recurrent tonsillitis and the development of systemic disease [17].

Establishment of the airway should be the corner stone of any management protocol followed by targeted treatment of the underlying cause of the infection. The majority of upper airway inflammatory processes are usually self-limiting. The general recommendations are that if a patient is not responding to first line management within 72 h, then the antibiotics regiment should be changed, combined with a vigorous search for the etiologic agent, including cultures, serologies or other molecular techniques. While empirical use of antibacterial agents, with all of its controversies, is widely practised, the routine use of anti-viral medications is not the norm. Even in neutropenic patients, antiviral drugs are not recommended for routine use unless clinical or laboratory evidence of a viral infection is apparent. Consequently, viral infections may advance before therapy is started. An upper respiratory tract infection may develop in up to 35 % of patients with aHUS, while viral infections, specifically infections with HSV, are described as a common side effect of Eculizumab treatment (in up to 10 % of patients), [18] even though approved by the Food and Drug Administration [19].

Conclusion

We presented two cases, one immunosuppressed patient and one immunocompetent patient, who under went tonsillectomies and were found to have unsuspected herpetic tonsillitis. The diagnosis must be included in the differential consideration clinically and histologically. Specifically, there should be an elevated index of suspicion in patients who are not responding to antibiotics or who are immunocompromised. Prompt diagnosis and appropriately targeted management can result in an excellent outcome with a shortened disease course.

References

1. Walker AE, Grimshaw JM, Armstrong EM. Salient beliefs and intentions to prescribe antibiotics for patients with a sore throat. Br J Health Psychol. 2001;6:347–60.
2. Putto A. Febrile exudative tonsillitis: viral or streptococcal? Pediatrics. 1987;80:6–12.
3. Taylor TJ, Brockman MA, McNamee EE, Knipe DM. Herpes simplex virus. Front Biosci. 2002;7:d752–64.
4. Whitley RJ. Herpes simplex virus infection. Semin Pediatr Infect Dis. 2002;13:6–11.
5. Chen T, Hudnall SD. Anatomical mapping of human herpesvirus reservoirs of infection. Mod Pathol. 2006;19(5):726–37.
6. Arduino PG, Porter SR. Herpes simplex virus type 1 infection: overview on relevant clinico-pathological features. J Oral Pathol Med. 2008;37:107–21.
7. Vassallo J, Camargo LA, Chagas CA, et al. Search for herpesvirus 1 and 2 by in situ hybridization in tonsils and adenoids. Int J Pediatr Otorhinolaryngol. 2005;69:345–9.
8. Karlidag T, Bulut Y, Keles E, et al. Presence of herpesviruses in adenoid tissues of children with adenoid hypertrophy and chronic adenoiditis. Kulak Burun Bogaz Ihtis Derg. 2012;22:32–7.
9. Brooke AE, Eveson JW, Luker J, Oakhill A. Oral presentation of a novel variant of herpes simplex infection in a group of bone marrow transplant patients: a report of five cases. Br J Dermatol. 1999;141:381–3.
10. Wat PJ, Strickler JG, Myers JL, Nordstrom MR. Herpes simplex infection causing acute necrotizing tonsillitis. Mayo Clin Proc. 1994;69:269–71.
11. Gonen C, Uner A, Cetinkaya Y, et al. Tonsillar abscess formation due to herpes simplex type-1 in a severely immunocompromised stem cell transplant patient with chronic myeloid leukemia. Transpl Infect Dis. 2006;8:166–70.
12. Tanaka N. Infection of herpes simplex virus (HSV) and Epstein–Barr virus (EBV) in acute tonsillitis—histopathological assessment by optical and electron microscopic observation of biopsy specimens of tonsils. Nihon Jibiinkoka Gakkai Kaiho. 2001;104:1093–102.
13. Strickler JG, Manivel JC, Copenhaver CM, Kubic VL. Comparison of in situ hybridization and immunohistochemistry for detection of cytomegalovirus and herpes simplex virus. Hum Pathol. 1990;21:443–8.
14. Rusan M, Klug TE, Henriksen JJ, et al. The role of viruses in the pathogenesis of peritonsillar abscess. Eur J Clin Microbiol Infect Dis. 2012;31:2335–43.
15. Young EJ, Vainrub B, Musher DM, et al. Acute pharyngotonsillitis caused by Herpesvirus type 2. JAMA. 1978;239:1885–6.
16. Espy MJ, Uhl JR, Mitchell PS, et al. Diagnosis of herpes simplex virus infections in the clinical laboratory by LightCycler PCR. J Clin Microbiol. 2000;38:795–9.
17. Sahin F, Gerceker D, Karasartova D, Ozsan TM. Detection of herpes simplex virus type 1 in addition to Epstein–Bar virus in tonsils using a new multiplex polymerase chain reaction assay. Diagn Microbiol Infect Dis. 2007;57:47–51.
18. Baxte S, Steid K, Probs L, Listman J. 19th Annual Meeting Abstracts: Treatment of atypical hemolyticuremic syndrome with Eculizumab in a 10 month old child. J Pediatr Pharmacol Ther. 2010;15:203–38.
19. Schrezenmeier H, Hochsmann B. Drugs that inhibit complement. Transfus Apher Sci. 2012;46:87–92.