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Clinical features of atypical presentations of mucocutaneous herpes simplex virus infection observed in immunosuppressed individuals. Part II: the knife-cut sign

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Abstract

The knife-cut sign is a distinctive manifestation of herpes simplex virus (HSV) type 1 or HSV type 2 infection that has been described in at least 10 immunocompromised patients. It appears as an extremely painful linear erosion or fissure in an intertriginous area such as the body folds beneath the breast, or within the abdomen, or in the inguinal region. Also, concurrent HSV infection at other mucocutaneous sites, or viscera, or both have been observed. The patients had medical conditions (at least 9 patients) and/or immunosuppressive drug therapy (6 patients). The diagnosis of HSV infection was confirmed by viral culture (8 patients), biopsy (4 patients), direct fluorescence antibody testing (3 patients), immunohistochemistry staining (2 patients), polymerase chain reaction (2 patients), or Western blot serologic assay (1 patient). Knife-cut sign-associated HSV infection is potentially fatal; three patients died. However, clinical improvement or complete healing occurred in the patients who received oral valacyclovir (1 patient), or intravenous acyclovir (2 patients), or intravenous acyclovir followed by foscarnet (1 patient). In summary, HSV infection associated with a positive the knife-cut sign is a potentially fatal variant of HSV infection that occurs in the intertriginous areas of immunocompromised patients and usually requires intravenous antiviral therapy.

Keywords: brain, Crohn, disease, encephalitis, Hermansky, herpes, herpetic, knife-cut, immunocompromised, neurosyphilis, Pudlak, sign, simplex, syndrome, virus

Introduction

Herpes simplex virus (HSV) infection presents as clinical lesions on the skin, the mucosa, or both. The morphology of the mucocutaneous lesions, particularly in immunocompetent individuals, commonly appears as small, erythematous-based vesicles that subsequently progress to erosions or superficial ulcers and then dried eschars that eventually are shed. However, the clinical presentation of a HSV infectious lesion can be variable—especially in an immunosuppressed patient [1-4].

Herpes simplex virus infection can present with atypical mucocutaneous presentations. The knife-cut sign is a unique morphologic manifestation of a HSV infectious lesion that always occurs in immunocompromised patients. The history of the knife-cut sign and the clinical features of this atypical presentation of HSV infection are discussed [5-30]. In addition, not only the clinical differential diagnosis of cutaneous linear fissures and erosions but also other medical conditions that are also characterized by the knife-cut sign are reviewed [10,22-58].

Discussion

The knife-cut sign is a distinctive clinical presentation of HSV infection. The painful lesions characteristically appear as a linear erosion or fissure in an intertriginous area. The knife-cut sign variant of HSV infection is potentially associated with patient mortality. The HSV infection may include

disseminated skin and/or visceral involvement and usually requires systemic treatment with intravenous antiviral therapy [22-68].

Knife-cut sign in medicine

The descriptive observation of a knife-cut sign in medical conditions has been attributed to several diseases including inflammatory bowel disease, infections, and a rare autosomal recessive genodermatosis (**Table 1**), [5-30]. Specifically, the sign was initially noted clinically on cutaneous examination, grossly on inspection of the affected bowel, and microscopically on pathology evaluation of involved tissue specimens in patients with Crohn disease. The sign has been used to describing not only the unique morphologic appearance of cutaneous HSV infection, but also a magnetic resonance imaging feature of brain HSV encephalitis;

in addition, the sign is also present on the brain magnetic resonance imaging of neurosyphilis. Lastly, the knife-cut sign—similar to that observed in Crohn disease—has been observed in the cutaneous lesion of mucocutaneous granulomatous disease associated with Hermansky-Pudlak syndrome.

Crohn disease

The skin manifestations of Crohn disease, a chronic granulomatous bowel disease, are characterized by non-specific—yet disease-related—conditions and specific granulomatous mucocutaneous lesions. The former include conditions such as erythema nodosum and pyoderma gangrenosum. Disease-specific lesions can result from either a direct extension of the affected colon to the skin or ‘metastatic’ lesions that are not contiguous with the bowel [8].

Table 1. *The knife-cut sign in medicine.*

Condition	Comment	Refs
Brain HSV encephalitis	MRI showing bilateral or asymmetrical mesiotemporal hyperintensities (observed as cortico-subcortical bright lesions, mostly in the mesiotemporal lobe), on the DWI and T2WI/FLAIR sequences is typically considered to indicate virtually pathognomonic herpes simplex virus encephalitis. Indeed, clear boundaries between the lesions and the outer edge of the lentiform nucleus are often shown in the MRI of viral encephalitis. These distinctive delineations of the boundaries have been described as the knife signs or knife-cut sign.	[5,6]
Brain neurosyphilis	A case report of a 51-year-old man with neurosyphilis whose MRI detected knife-cut signs (presenting as cortico-subcortical bright lesions mostly in the mesiotemporal lobe, in addition to the frontotemporal and parietal lobes, hippocampus, and thalamus as well as signal hypertensity in the left insular cortices on the DWI and T2WI/FLAIR sequences.	[5]
Crohn disease	Metastatic Crohn disease (also referred to as cutaneous Crohn disease) presents with mucosal or cutaneous lesions at sites that are not contiguous with the intestines. Genital lesions involving the vulva and the inguinal folds can appear as deep longitudinal fissures and erosions similar in appearance to skin or mucosal site being cut with a knife (and therefore referred to as the knife-cut sign). In addition, not only the gross morphology of the mucosal lesions of the intestine but also the associated pathology changes seen on light microscope examination of the affected tissue have the appearance of a knife-cut.	[7-21]
Cutaneous HSV infection	HSV infection, in some immunocompromised patients, have the appearance of a deep linear erosion or ulcer morphologically similar to the appearance of skin after a knife-cut. These HSV-associated lesions are typically located in body folds, such as the inguinal folds or abdominal folds or inframammary folds; they also appeared in the concave area between the scalp and the external ear.	[22-28]
HPS-associated MGD	Clinical images and description of the bilateral knifelike flexural ulceration of the inguinal folds, typical of genital metastatic cutaneous Crohn disease, was provided in the case report of a woman who had HPS and MGD. Less severe genital lesions (erosions of both labia majora) and peristomal ulcers of MGD has also been reported in a 9-year-old Puerto Rican girl with HPS. The morphology and pathology of HPS-associated MGD is indistinguishable from metastatic Crohn disease.	[29,30]

DWI, diffusion weighted image; MGD, mucocutaneous granulomatous disease; HPS, Hermansky-Pudlak syndrome; FLAIR, fluid-attenuated inversion recovery; HSV, herpes simplex virus; MGD, mucocutaneous granulomatous disease; MRI, magnetic resonance imaging; Refs, references; T2WI, T2-weighted images.

The first descriptions of the non-contiguous skin lesions of Crohn disease were by Parks et al., at the dermatology section of the Royal Society of Medicine in 1965, during their case presentation of a 70-year-old woman with inguinal and submammary Crohn-related cutaneous lesions [16,59]. During the subsequent discussion, Dr. Morson mentioned another patient at St Mark's Hospital in whom "...a skin lesion has been found remote from the gastrointestinal tract and separated from the latter by normal skin" [16]. Dr. Jarrett subsequently commented that "...these [skin lesions] are in the nature of metastases" [16], thereby introducing the term 'metastatic Crohn's disease' into the medical lexicon.

The designation of the knife-cut sign in cutaneous Crohn disease was coined in 1993. In the introduction of their case report, Shen et al. stated that "...vulvar ulceration in Crohn disease is rare and most commonly reported as deep ulcerations which give rise to a characteristic 'knife-cut' appearance of the vulva..." [7]. However, the morphology of vulvar metastatic Crohn disease is pleomorphic and also includes edema [60,61], folliculitis [62] hypertrophy [63,64], indurated swelling [61,65,66], pustules [60,61], and ulcers that are either deep [62] or herpetiform [7] or small, shallow, and superficial [11,62,67].

Prior and subsequent to the original description of the knife-cut sign, other researchers had described this vulvar manifestation of Crohn disease [8-15]; however, there are several other conditions in which vulvar fissures can be observed [15]. Indeed, similar appearing ulcerative, often linear, lesions were noted in body folds of the abdomen and beneath the breasts [14,16-18]. Albeit less common, in addition to women, similar metastatic Crohn disease cutaneous lesions with a knife-cut sign were also noted in the inguinal folds of men [17,18].

The knife-cut sign has also been used to refer to not only the gross appearance of Crohn disease-affected bowel [8,9,19-21], but also the pathology changes demonstrated on microscopic examination of tissue specimens from these patients [8,9,21]. In addition to surgical specimens of colon, proctoscopic, sigmoidoscopic, and colonoscopic examination of

the involved bowel mucosa in a patient with Crohn disease show skip lesions and colon with a cobblestone pattern of normal areas of mucosa outlined by longitudinal linear mucosal ulcers or fissures (with a knife-cut appearance) and extensive anastomosing ulcers [8,9,19-21]. In addition, histopathologic evaluation of resected bowel mucosa shows transmural—acute and chronic— inflammation, noncaseating granulomas, and knife-like deep ulcers and linear fissures [8,9,21].

Cutaneous HSV infection

Mucocutaneous manifestations of HSV infection, particularly in immunosuppressed individuals, can have unique morphologic appearances. Geometric fissures of the tongue have been observed [68]. In addition, similar to the knife-cut presentation of the clinical lesions in some of the patients with metastatic Crohn disease, deep, HSV culture-positive, linear erosions, fissures, and ulcers predominantly in intertriginous areas have been noted—and described as a positive knife-cut sign—in HSV infected patients who were immunocompromised or had multiple medical morbidities [22-28].

Hermansky-Pudlak syndrome-associated mucocutaneous granulomatous disease

Hermansky-Pudlak syndrome is an autosomal recessive condition characterized by decreased pigmentation (oculocutaneous albinism), platelet abnormality-associated bleeding problems, and lysosomal ceroid lipofuscin accumulation [69,70]. There are eight classic forms which can result from mutations in several different genes; depending of the etiology, patients can have Hermansky-Pudlak syndrome-related pulmonary fibrosis or inflammatory bowel disease (referred to as either mucocutaneous granulomatous disease or granulomatous colitis), [58,71]. The clinical presentation and pathology changes of mucocutaneous granulomatous disease is identical to Crohn disease; hence, the knife-cut sign has been described in these patients [29,30].

Magnetic resonance imaging changes attributed to HSV encephalitis and neurosyphilis

Knife signs or knife-cut sign has not only been observed on the magnetic resonance image of the

brain as a pathognomonic feature of encephalitis associated HSV infection, but also more recently in a patient with neurosyphilis [5,6]. It appears as a distinctive delineation of the boundary between virus-associated lesions and the outer edge of the lenticular nucleus in patients with herpes simplex virus-related encephalitis [5,6]. In the man with neurosyphilis, it presented as cortico-subcortical bright lesions [5].

History of cutaneous HSV-related knife-cut sign

In 1992, Koutsky et al. reported their observations from a retrospective evaluation of the ability of type-specific serologic methods to identify not only recurrent HSV type 2 infection, but also unrecognized or subclinical HSV infection in women who attended a sexually transmitted disease clinic [22]. The investigators included an image of a woman who had vulvar fissures caused by HSV type 2 infection [22]. Subsequent researchers, after reviewing this paper, have acknowledged that these clinical features demonstrated those of HSV infection-related knife-cut sign (**Table 2**), [22-28].

Lieb et al., 16 years later in 2008, introduced the term knife-cut sign to describe the distinctive morphologic appearance of the intertriginous and vaginal erosive linear HSV infection-associated fissures they had noted in three immunocompromised women [23]. They emphasized that the presentation of these deep linear ulcers was clinically indistinguishable from those observed in patient with extraintestinal metastatic Crohn disease. Subsequently, two years later in 2010, some of the same researchers described another woman with corticosteroid-related immunosuppression and multiple medical problems who also had this manifestation of HSV infection [24].

Five years thereafter, in 2015, Cohen reported a man with multiple myeloma-related immunosuppression who developed HSV infection with a positive knife-cut sign not only in the intertriginous areas of his inguinal folds, but also bilaterally at the base of the supra-auricular skin folds between his ear and head [25]. The features of this man and the four prior women with this unique presentation of HSV infections were summarized. The paper concluded that when an immunocompromised individual

presented with the new onset of linear ulcers in intertriginous areas and body folds suggestive of the knife-cut sign, the clinician should consider the possibility of a cutaneous HSV infection and promptly initiate systemic antiviral therapy—even prior to receiving laboratory confirmation of the suspected diagnosis [25].

In 2022, another immunosuppressed woman and three patients with multiple medical morbidities (including two women and one man) with HSV infection knife-cut sign were described respectively by Attah et al., and Millan et al., [26,27]. The next year, in 2023, Konda et al. provided a retrospective study of HSV infection in pemphigus vulgaris patients; either HSV-associated linear cutaneous and/or oral erosions (8 patients) or skin fissures (6 patients) were observed [28]. In 2023, Cohen reviewed the world literature regarding the characteristics of patients who had a positive knife-cut sign that was caused by a cutaneous HSV infection.

Epidemiology

The knife-cut sign of cutaneous HSV infection has been reported in at least 10 individuals: 8 women and two men. The patients ranged in age from 22 years to 74 years (median, 61 years). The women ranged in age from 22 years to 74 years (median, 66 years); the men were 57 years old, and 61 years old (**Table 3**), [22-28].

Race was described in three patients. Two women were African American. One man was Hispanic [22-28].

Medical diseases

At least 9 patients with HSV whose lesions have the knife-cut sign had two or more comorbid medical conditions. Diseases present in more than one person included chronic kidney disease or end-stage renal disease (4 patients), infection (4 patients), morbid obesity (3 patients), cerebrovascular accident (2 patients), drug reactions (2 patients), hypertension (2 patients), malignancy (2 patients), seizures (2 patients), and systemic lupus erythematosus (2 patients), [22-28].

Immunosuppressive treatment

Two-thirds of the individuals (6 of 9 patients) with knife-cut sign-associated HSV infection were receiving an immunosuppressive drug. The patients

Table 2. History of cutaneous herpes simplex virus-related knife-cut sign.

Author (Year)	Comment	Ref
Koutsky et al. (1992)	A retrospective study of 779 women attending a sexually transmitted disease clinic concluded that women with recurrent HSV-2 infection, as well as those with unrecognized or subclinical infection, can be identified with type-specific serologic methods. In the results section, the figure demonstrates one woman with HSV-2-related vulvar fissures	[22]
Lieb et al. (2008)	The first paper to introduce the knife-cut sign to describe the linear erosive HSV infection presenting as intertriginous (inguinal fold, intra-abdominal fold, and inframammary) and vaginal fissures in three immunocompromised women	[23]
LeBoeuf et al. (2010)	The second paper to refer to linear erosive HSV infection of the abdominal and inguinal folds, the gluteal crease, and the interlabial sulci of a woman with multiple medical conditions and high-dose corticosteroid-induced immunosuppression as the knife-cut sign	[24]
Cohen (2015)	A case report of an immunocompromised man with HSV infection presenting with the knife-cut sign; his viral lesions were located bilaterally on his inguinal folds and supra-auricular curve between his external ear and scalp	[25]
Attah et al. (2022)	A case report of a immunosuppressed woman with HSV infection-related linear ulcerations (knife-cut sign) on the left breast and bilateral inframammary regions, inguinal folds, and perineal regions.	[26]
Millan et al. (2022)	A case series of two women and one man with multiple medical comorbidities and HSV infection-related intertriginous linear ulcers (knife-cut sign) in the abdominal fold (of all three patients) and the inguinal fold (of the man)	[27]
Konda et al. (2023)	A retrospective study of the incidence and morphology of HSV infection in 60 pemphigus vulgaris patients. HSV-associated linear erosions were seen on the skin and oral mucosa of eight patients; however, linear erosions were also seen in one patient without HSV infection. In addition, HSV-related fissures in the skin were observed in six patients; however, skin fissures were not observed in patients without HSV infection	[28]
Cohen (2024)	A comprehensive evaluation of reported patients with knife-cut sign-associated HSV infection is summarized. The history, presenting symptoms and lesion features, management and differential diagnosis of this uncommonly described manifestation of HSV infection are discussed	CR

CR, current report; HSV, herpes simplex virus; HSV-2, herpes simplex virus type 2; Ref, reference.

were either receiving one drug (2 patients), two medications (2 patients), three therapies (1 patient) or four agents (1 patient). Five patients were receiving a systemic corticosteroid [22-28].

Immunocompromised patients

All patients with knife-cut sign mucocutaneous HSV lesions were immunocompromised. The immunosuppression was associated with their underlying medical conditions, or the systemic agents they are receiving, or both [22-28].

Diagnosis of HSV infection

All the patients with HSV infection-related knife-cut skin lesions had one or more diagnostic tests that established the diagnosis. These included positive microscopic examination of a biopsy specimen of the lesion which showed multinucleated epidermal giant cells (4 patients), positive viral culture for herpes virus (4 patients), positive direct fluorescence antibody testing for herpes virus (3 patients), positive immunohistochemistry staining of a tissue

lesion biopsy specimen for herpes virus (2 patients), positive polymerase chain reaction for herpes virus (2 patients), and positive serologic assay using Western blot testing for herpes virus (1 patient), [22-28].

Herpes simplex virus type 1 was isolated in four patients. Herpes simplex virus type 2 was also isolated in four patients. The specific HSV serotype was not determined in two patients [22-28].

Clinical presentation

The HSV infection lesions with a positive knife-cut sign have also been referred to as knife-cut linear erosions, knife-cut intertriginous ulcers, knife-cut ulcerations, and knife-cut HSV lesions [27]. Morphologically, the lesions were similar to those observed in patients with Crohn's disease; however, in some of the patients with knife-cut sign HSV lesions, the infectious viral lesions were more extensive and exaggerated in appearance [22-28].

The knife-cut sign-positive HSV infection lesions present as linear or longitudinal fissures and ulcers; initially, the clinical impression is consistent with the changes that would be observed if a sharp knife blade was used to slice the skin—to a depth of the deep dermis—and the wound edges were then permitted to spread. Subsequently, the superficial fissures and erosions may develop into deeper ulcers. The clinical differential diagnosis of knife-cut sign-positive HSV infection lesions includes other conditions that may have linear fissures or erosions (**Box 1**), [10,24,29-58].

Herpes simplex virus-associated lesions with a positive knife-cut sign were most commonly located in intertriginous areas or body folds or both. The



Figure 1. A) Distant, and **B)** closer views of knife-cut sign-positive linear erosive herpes simplex virus infection affecting the bilateral inguinal folds. A 57-year-old immunosuppressed Hispanic man had a history of multiple myeloma; he had been treated with several stem cell transplants. His clinical course had not only been complicated by cutaneous graft-versus-host disease (which was managed with extracorporeal photophoresis, prednisone, rituxan, and sirolimus), but also various infections from fungi (*Aspergillus*), mycobacteria (*Mycobacteria kansasii*), and viruses (including recurrent oral herpes simplex virus and reactivation of both Epstein-Barr virus and cytomegalovirus). He recently had been hospitalized, one month earlier, for *Pseudomonas aeruginosa*-associated eczematous auricular dermatitis and a viral culture-positive (subsequently discovered acyclovir-resistant) herpes simplex virus type 1 lateral tongue ulcer; prior to receiving the culture sensitivity, the ulcer was treated by increasing his oral acyclovir dose. His current hospitalization was for evaluation and treatment of fever, neutropenia, and cutaneous erosions and ulcers located on his face (malar cheeks, columella of the nose, nasal tip, and oral commissures), shoulders, back, legs, suprapubic area, scrotum, and penile shaft. In addition, both inguinal folds had large linear ulcers, suggestive in appearance of a 'knife-cut'; a skin biopsy showed multinucleated epidermal giant cells and both the direct fluorescent antibody test and viral culture were positive for herpes simplex virus type 1. (Reproduced with permission. Cohen PR. The "knife-cut sign" revisited: a distinctive presentation of linear erosive herpes simplex virus infection in immunocompromised patients. *J Clin Aesthet Dermatol.* 2015;8:38-42 [25]).

most common site was the bilateral inguinal folds in 6 patients: both men and four women (**Figure 1**). The next location that was frequently affected was the skin at the base of the abdominal folds in one man and four women. Lesions were also noted within the inframammary folds—either unilateral or bilateral—of two women. Viral-related knife-cut lesions in women were also observed in the gluteal cleft, the interlabial sulcus, the perineal region, the vagina, and the vulva. One man had knife-cut HSV lesions at the base of the supra-auricular fold created by his external ear and the adjacent scalp (**Figure 2**), [22-28].

Four women only had knife-cut HSV lesions. However, 5 patients had disseminated HSV infection with between two to 9 (median, 4) additional mucosal and/or cutaneous sites of viral lesions. The buttock, genital (including scrotum and penile shaft), legs, and mons pubis or suprapubic, were affected in four patients. Other locations, each only in one patient, included the abdomen, back, face, flank, genitals, inguinal folds, mons pubis, mouth, nose, shoulder, skin overlying the ischial processes, and vulva. The additional sites of HSV infection were not described in one patient [22-28].

Two patients had disseminated HSV infection that affected visceral sites. One patient was a 61-year-old

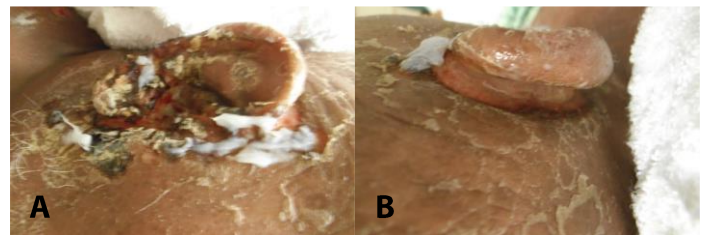


Figure 2. A) Distant, and **B)** closer views of knife-cut sign-positive linear erosive herpes simplex virus infection affecting the bilateral supra-auricular folds between the external ear and the scalp. The direct fluorescent antibody test and viral culture of the linear, 'knife-cut' appearing, ulcers in the man's curved supra-auricular fold were also both positive for herpes simplex virus type 1. He was initially treated with intravenous antibiotics (for a possible recurrent *pseudomonas* infection) and acyclovir; however, when the sensitivities from the viral culture from his prior hospitalization were received, the acyclovir was intravenous foscarnet. During the next 10 to 14 days, all his ulcers demonstrated clinical improvement. (Reproduced with permission. Cohen PR. The "knife-cut sign" revisited: a distinctive presentation of linear erosive herpes simplex virus infection in immunocompromised patients. *J Clin Aesthet Dermatol.* 2015;8:38-42 [25]).

man with knife-cut lesions on his abdominal fold and inguinal folds, numerous cutaneous virus-related ulcers at other skin sites including his buttocks, flanks, genitals, and legs; his cerebrospinal fluid was also positive for HSV [27]. The second patient was a 73-year-old woman with knife-cut positive viral lesions bilaterally located in her inframammary folds, inguinal folds, and perineal region; in addition, she had elevated liver function tests—consistent with viral hepatitis—that improved with antiviral therapy [26].

Treatment

The management of knife-cut sign-positive HSV infection lesions was described for 9 of the patients. All 9 individuals received an antiviral agent either topically (1 patient), orally (4 patients), or intravenously (4 patients). Six patients were treated with acyclovir and three patients were treated with valacyclovir [22-28].

The woman treated with topical acyclovir died four days after starting therapy [23]. The woman treated with oral acyclovir was lost to follow-up [23]. Oral valacyclovir was received by three women; one died after 10 days of treatment [26], one experienced clinical improvement after four days and continued treatment for three weeks [23], and one did not have her response to therapy reported [27].

Intravenous acyclovir was received by four patients. Two patients had complete healing [24,27] and one woman died from septic shock [27]. The fourth patient had a prior episode of acyclovir-resistant HSV infection and developed the knife-cut sign-positive lesions while receiving intravenous acyclovir; clinical improvement occurred after his treatment was changed to intravenous foscarnet [25].

Response to therapy

Herpes simplex virus infection lesions with a positive knife-cut sign is a severe and serious condition. It always occurs in patients who are immunocompromised and frequently presents as a HSV infection with disseminated skin lesion (4 patients) or visceral organ involvement (1 patient) or both (1 patient). The patients were typically hospitalized for the treatment of one or more concurrent medical conditions; indeed, 43 percent of

the patients (3 of 7 individuals) died during the management of their HSV infection [22-28].

Clinical improvement or complete healing was observed in four patients who were treated with systemic antiviral therapy. Complete healing occurred in two patients who received intravenous acyclovir. Clinical improvement was noted after treatment with oral valacyclovir (1 patient) or after changing therapy from intravenous acyclovir to intravenous foscarnet in a man who had a previous acyclovir-resistant HSV infection [22-28].

Conclusion

The knife-cut sign is a unique manifestation of HSV infection. It appears as an exquisitely painful linear erosion or fissure in an intertriginous area. In addition to being a distinctive clinical stigmata of HSV infection, the knife-cut sign has also been used to describe not only the clinical morphology of skin and mucosal lesions in metastatic Crohn disease and Hermansky-Pudlak syndrome-associated mucocutaneous granulomatous disease, but also the pathognomonic changes observed on the magnetic resonance imaging examinations of the brain in patients with HSV encephalitis and neurosyphilis. Vulvar fissures of HSV-associated knife-cut sign was initially reported in a study that was published in 1992; however, it was not until 2008 that investigators used the term knife-cut sign to describe this clinical variant of HSV infection. To date, cutaneous HSV infection-related knife-cut sign has been reported in at least 10 immunocompromised individuals: 8 women and two men. Concurrent or prior medical conditions were present in at least 9 of the patients and treatment with immunosuppressive agents were present in 6 patients. Viral culture confirmed the presence of HSV type 1 (4 patients) or HSV type 2 (4 patients). Biopsy—with (2 patients) or without (2 patients) immunohistochemistry staining—was also used to establish the diagnosis. In addition, either direct fluorescence antibody testing (3 patients), polymerase chain reaction (2 patients), or Western blot serologic assay (1 patient) were positive for HSV infection. In addition to intertriginous areas (such as the body

folds beneath the breast, or within the abdomen, or in the inguinal region) and the base of the fold created by the external ear and the adjacent scalp, four patients had other sites of mucocutaneous HSV infection, one patient had disseminated HSV infection to the liver, and one patient had disseminated HSV infection to not only other mucocutaneous locations but also to the cerebrospinal fluid. Management of the patients with knife-cut sign HSV infection was described in 9 patients: topical acyclovir (1 patient), oral acyclovir (1 patient) or valacyclovir (3 patients), and intravenous acyclovir—only (3 patients) or followed by foscarnet to treat acyclovir-resistant HSV infection (1 patient). This is a potentially fatal variant of HSV infection; three of 7 patients, in whom the response to treatment was described, died. The four patients—who received either oral valacyclovir (1 patient), or intravenous acyclovir (2 patients) or intravenous acyclovir followed by foscarnet (1 patient)—

experienced clinical improvement or complete healing. In summary, the knife-cut sign is a distinctive variant of HSV infection that occurs in the intertriginous areas of immunocompromised patients. However, it can be not only restricted to the knife-cut sign sites but also disseminated to other mucocutaneous location, visceral organs, or both. Systemic antiviral therapy—usually administered intravenously—is necessary for treatment since nearly half of the patients who have HSV infection associated with a positive knife-cut sign died.

Potential conflicts of interest

Dr. Cohen is a consultant for ParaPRO; however, this activity has no influence as a potential conflict of interest with regards to the manuscript. Therefore, the author declares no conflicts of interest.

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Table 3. Characteristics of patients with cutaneous herpes simplex virus-related knife-cut sign^a.

C	A R S	Medical Diseases ITx	IC	Dx of HSVI HSV Sero	K-C lesion sites Other HSVI sites	Treatment	Response to treatment	Refs
1	22 AA F	Sap, SLE HC, Pred	+	Dfa- VC+ HSV-2	IF (Bi), VF None	PO Acy: dose NS	LtF	[23], C2
2	42 AA F	AS, Cal, ESRD HD	+	Dfa+ HSV-1	IMF (L) None	Top Acy: QID for 4 days	Died (4 days after start Tx)	[23], C1
3	53 NS F	SBP, TB None	+	Bx+ ^b Dfa- VC- HVI	AbdF, IF (Bi) None	PO Val: 1 gram TID for 3 weeks	CI after 4 days of Tx	[23], C3
4	57 Hp M	GVHD, MM ECPP, Pred, Ritux, Sir	+	Bx+ ^b Dfa+ VC+ HSV-1	IF (Bi), SA (Bi) Ba, Fa, Le, Mo No, PS, Sc, Sh, Sp	IV Acy, IV Fos	CI: 10 to 14 days after start IV Fos ^c	[25]
5	61 NS M	CKD, MO, PVD, SDD None	+	Bx+ ^b IHC+ ^d PCR+ HSV-2	AbdF, IF But, CSF, Fl, Gn, Le	IV Acy	Complete healing	[27], C1
6	66 NS F	AF, CVA, AVM, DRESS, LO, Se Mpred	+	Dfa+ VC+ HSV-1	AbdF, GC, IF (Bi), ILS None	IV Acy	Complete healing	[24]
7	72 NS F	CCD, CVA, DIR, ESRD, GMS, HIT, IE, MO HD, Cortico	+	PCR+ HSV-1	AbdF, IF But, IP	IV Acy	NS; died from septic shock	[27], C2
8	73 NS F	CKD, Dep, HTN, RA, SLE HC, MTX, Pred, Ritux	+	Bx+ ^b IHC+ ^d HVI	Bi: IMF, IF, PR Liver	PO Val for 10 days	Minimal CI; pt died	[26]
9	74 NS F	BC, DM, DVT, HTN, MO, PE None	+	PCR+ HSV-2	AbdF(L) Abd, IF, MP, vulva	PO Val: BID for 7 days	NS	[27], C3
10	NS NS F	NS NS	NS	SAs+ VC+ HSV-2	Vulva +, NS	NS	NS	[22]

^aA retrospective study of clinical markers of HSVI was performed in 60 patients with pemphigus vulgaris. HSVI was present in 23 patients; patients had one or more clinical presentations of HSVI. Linear erosions of the skin or oral mucosa or both were noted in eight patients and fissures in the skin were observed in 6 patients. The descriptive morphology of these lesions is compatible with the knife-cut sign; however, additional details were not provided by the investigators [28].

^bMultinucleated epidermal giant cells, consistent with a HVI, were observed.

^cInitially IV Acy (10 milligrams per kilogram every 8 hours); however, VC+ for Acy-resistant HSV. Changed to IV Fos (45 milligrams per kilogram every 8 hours); all lesions improved during next 2 weeks.

^dThe combined IHC for HSV-1 and HSV-2 was positive; the IHC for varicella zoster virus was negative.

A, age in years; AA, African American; Abd, abdomen; AbdF, abdominal fold; Acy, acyclovir; AF, atrial fibrillation; AS, Asherson's syndrome (catastrophic antiphospholipid syndrome); AVM, arteriovenous malformation; Ba, back; Bi, bilateral; BC, breast cancer (status post lumpectomy); But, buttocks; Bx, biopsy; C, case; Cal, calciphylaxis; CCD, chronic cognitive dysfunction; Cl, clinical improvement; CKD, chronic kidney disease; Cortico, corticosteroids; CSF, cerebrospinal fluid; CVA, cerebrovascular accident; Dep, depression; Dfa, direct fluorescence antibody test; DIR, drug-induced rash; DM, diabetes mellitus (type 2); DRESS, drug rash with eosinophilia and systemic symptoms; Dx, diagnosis; DVT, deep vein thrombosis; ECPP, extracorporeal photophoresis; ESRD, end stage renal disease; F, female; Fa, face; Fam, famciclovir; Fl, flanks; Fos, foscarnet; GC, gluteal cleft; GMS, grand mal seizures; Gn, genitals; GVHD, graft-versus-host disease (cutaneous); HC, hydroxychloroquine (oral); HD, hemodialysis; HIT, heparin-induced thrombocytopenia; Hp, Hispanic; HSV, herpes simplex virus; HSV-1, herpes simplex virus-type 1; HSV-2, herpes simplex virus-type 2; HSVI, herpes simplex virus infection; HTN, hypertension; HVI, herpes virus infection; IC, immunocompromised; IE, infective endocarditis; IF, inguinal fold; IHC, immunohistochemical stain; ILS, interlabial sulcus; IMF, inframammary fold; IP, ischial processes (skin overlying); ITx, immunosuppressive treatment; IV, intravenous; K-C, knife-cut; L, left; Le, legs; LO, lumbar osteomyelitis (with disc-space cultures positive for methicillin-resistant *Staphylococcus aureus* and *Clostridium paraputrificum*); LtF, lost to follow-up; M, male; MD, medical diseases; MM, multiple myeloma; Mo, mouth; MO, morbid obesity; MP, mons pubis; Mpred, methylprednisolone (intravenous); MTX, methotrexate; No, nose; NS, not stated; PE, pulmonary embolism; PO, oral; Pred, prednisone (oral); PR, perineal region; PS, penile shaft; pt, patient; PVD, peripheral vascular disease; SAP, *Staphylococcus aureus* pustulosis; QID, four times daily; R, race, RA, rheumatoid arthritis; Refs, references; Ritux, rituximab; S, sex; SA, supra-auricular curved fold between the external ear and the scalp; SAs, serology assay (Western blot analysis); SBP, spontaneous bacterial peritonitis; Sc, scrotum; SDD, severe developmental delay; Se, seizures (progressing to status epilepticus); Sero, serotype; Sh, shoulders; Sir, sirolimus; SLE, systemic lupus erythematosus; SP, suprapubic; TB, tuberculosis (pulmonary and peritoneal, which was incompletely treated because of medication-induced hepatitis); TID, three times daily; Top, topical; Tx, therapy; Val, valacyclovir; VC, viral culture; VF, vaginal fissures; +, positive; -, negative.

This table has been modified and reproduced with permission. Cohen PR. The "knife-cut sign" revisited: a distinctive presentation of linear erosive herpes simplex virus infection in immunocompromised patients. *J Clin Aesthet Dermatol.* 2015;8:38-42 [25].

Box 1. *Differential diagnosis of cutaneous linear fissures and erosions.*

Dermatitis

Atopic dermatitis [10,24]
 Bettle dermatitis [31]
 Contact dermatitis [24]
 Lichen simplex chronicus [10]
 Neurodermatitis [10]
 Pompholyx [32]
 Seborrheic dermatitis [24]

Hormone (drug) associated

Inadequate tissue estrogen levels^a [10]

Infections

Candida [10,24,32]
 Group B streptococcus [10,24]
 Granuloma inguinale [10,24]
 Herpes simplex virus [22-28]
 Leprosy [34]
 Staphylococcus [24]

Infestations

Scabies (scabies serrupticius, hyperkeratotic variant) [35-37]

Inflammatory bowel disease

Crohn disease [10,38,39]

Metabolic diseases

Diabetes mellitus (foot fissures) [40,41]

Miscellaneous skin conditions

Congenital erosive and vesicular dermatosis [42]
 Drywall stilt dermatosis [43]
 Idiopathic (heel fissures) [44]
 Lichen sclerosus (vulvar) [24,45]

Neoplastic conditions

Langerhans cell histiocytosis [24]

Papulosquamous conditions

Linear porokeratosis [46]
 Psoriasis [24]

Psychocutaneous diseases

Dermatitis artefacta [47,48]
 Neurotic excoriations [49]

Syndromes

Amniotic band syndrome [50,51]
 Curracino syndrome [52]
 Dyskeratosis congenita [53]
 Harlequin ichthyosis (ichthyosis fetalis) [54-57]
 HPS-associated MGD [29,30,58]

Trauma

Coitus-associated thrusting trauma^b [10]
 Exogenous (knife cut)

^aThe causes of low tissue estrogen levels include oral contraceptive use, being postpartum, and being postmenopausal.

^bThe posterior portion of the vulvar vestibule is defined by a fold of skin that is formed where the posterior portions of the labia minora unite; this fold can be both prominent and taut in some women. As a result of thrusting trauma, this fold can tear during coitus and thereby create a linear fissure. HPS, Hermansky-Pudlack syndrome; MGD, mucocutaneous granulomatous disease