

ORIGINAL RESEARCH

Chronic erosive herpes simplex virus infection of the penis, a possible immune reconstitution disease

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Objective

To report a novel clinical presentation: a chronic erosive herpes simplex virus (HSV) infection of the penis which developed in AIDS patients following the commencement of highly active antiretroviral therapy (HAART). The lesions were unresponsive to antiviral treatments which had previously been effective, and this could not be accounted for in terms of increased antiviral resistance.

Design

Detailed case-note review and investigation of three cases which presented at two large HIV units in London.

Methods

Review of all histology with immunohistochemistry for HSV, HSV drug susceptibility assays, tissue typing and measurement of *in vitro* lymphocyte functional activity against HSV.

Results

The histology of the lesions was the same in each case, with the presence of HSV on immunohistochemistry and an unusual prominence of plasma cell and eosinophils in the inflammatory infiltrate. HSV-specific lymphoproliferative responses were normal in two cases, but subnormal in a third case. All individuals shared the HLA class I molecules B72 and Cw0202 and the class II allele DRB4.

Conclusion

We believe this to be a previously unreported adverse consequence of HAART, the result of partial immune restoration, reminiscent of the the recently described syndrome of immune recovery vitritis.

Key words: antiviral therapy, dermatology, HAART, histopathology, HSV

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Introduction

Herpes simplex virus (HSV) infection is common in subjects infected with HIV, and is the cause of widespread morbidity [1]. Indeed, early in the epidemic, chronic mucocutaneous HSV infection was recognized as a presenting feature of AIDS [2]. The use of aciclovir has proved to be highly efficacious in such cases, although in

recent years the emergence of aciclovir-resistant HSV has necessitated the use of intravenous foscarnet as an alternative [3,4].

We report a novel clinical presentation: three cases of refractory penile erosion in black Ugandans with AIDS. Each had a prior history of genital HSV, but after initiation of highly active antiretroviral therapy (HAART) a dramatic clinical picture developed: a chronic erosive HSV infection which was unresponsive to antiviral treatments which had previously been effective.

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Case 1

A 32-year-old HIV-1 positive man with AIDS presented in August 1996 with an uncomfortable preputial erosion without palpable inguinal lymph nodes. He had been diagnosed as having AIDS on the basis of oesophageal candidiasis 3 years previously, when his CD4 lymphocyte count was 12 cells per mm³, but he had only agreed to commence on HAART 8 weeks before the erosion began. His CD4 count at this time was still 12 cells per mm³, and the antiretrovirals selected were stavudine, lamivudine and indinavir. By October 1996, 6 weeks after presentation, his CD4 lymphocyte count had risen to 48 cells per mm³.

Initial investigation revealed the presence of HSV type-2. Despite a persistently low CD4 count, this was only his second recurrence of genital herpes following a confirmed primary episode in 1994. The first recurrence was in July 1996, very shortly after starting HAART, and responded rapidly to a standard dose of aciclovir 200 mg q.q.h. for 5 days.

The second recurrence was unusual because of its failure to heal after 4 weeks' treatment with oral aciclovir, raising

the possibility of some alternative underlying cause. Further investigations were undertaken, as follows.

Biopsy showed erosion of the mucosa with an underlying inflammatory infiltrate as described under histopathology. Skin cultures to detect mycobacterial and fungal pathogens were negative, and bacterial culture showed only scanty mixed commensal organisms.

Repeated dark ground illumination for *Treponema pallidum* was negative. Syphilis serology showed a positive *Treponema pallidum* haemagglutination assay (TPHA) with a negative venereal diseases research laboratory assay (VDRL), consistent with a known history of yaws infection in childhood. Serological testing for the *Chlamydia trachomatis* serovars responsible for lymphogranuloma venerium was negative.

On the basis that he might have aciclovir-resistant HSV, he was admitted 2 months later for intravenous foscarnet. After 10 days of this therapy there was considerable improvement of his lesions. Subsequent treatment with oral valaciclovir 1 g t.i.d. failed to maintain the improvement. Circumcision was performed in December 1996 but was not curative. Multiple erosions were present on the circumcision sample. Analysis showed cells at the bases of

Table 1 Case 1 summary

1993	AIDS (oesophageal candida)	CD4 count 12 per mm ³
1994	Primary HSV	
1996 end June	Commenced HAART	CD4 count 1 per mm ³
1996 July	First HSV recurrence	CD4 count 12 per mm ³
	Oral aciclovir 5 days: complete response	
1996 August	Unusual HSV lesion	
	Oral aciclovir 4 weeks: no response	
1996 October	i.v. foscarnet 10 days: partial response	CD4 count 48 per mm ³
1996 November	Trimovate cream 4 weeks: no response	
1996 December	circumcision	
1997 January	Oral aciclovir, then valaciclovir for 4 weeks:	
	no response	
1997 February	Trimovate cream plus i.v. foscarnet for	IC ₅₀ aciclovir 2.8 mM,
	4 days then i.v. cidofovir for 21 days:	foscarnet 104 µM
	no response	CD4 count 175 per mm ³
1997 April	Topical gentian violet and varidase:	
	no response	
1997 June	HAART discontinued	CD4 count 242 per mm ³
1997 August	Topical 2% eosin in water: no response	
1997 September	Topical foscarnet and idoxuridine in	
	DMSO: no response	
1997 October	Topical trifluridine: no response	
	HAART recommenced	
1997 December	i.v. foscarnet for 2 weeks then topical	CD4 count 193 per mm ³
	foscarnet 1%: partial response	HIV viral load below detection
1998 February	Topical cidofovir 1%: slow healing of	CD4 count 230 per mm ³
	lesions begins	HIV viral load below detection
1998 June	All lesions healed	CD4 count 254 per mm ³
1998 September	HSV lesion on palate: still present	CD4 count 260 per mm ³
	in March 1999	HIV viral load below detection.

the erosions with the typical intracellular changes of HSV infection [5] and the presence of HSV was confirmed by immunohistochemistry.

In February 1997 intravenous foscarnet was again administered, but after 4 days had to be discontinued because of pyrexia. Intravenous cidofovir was substituted, but after 3 weeks of treatment was discontinued due to rising creatinine levels.

Viral resistance studies, received in June 1997, exhibited no resistance of the HSV to any of the antiviral agents that had been used (see Table 1) The possibility that this was a fixed drug eruption, and that the HSV was only secondarily involved, was considered. Unfortunately, discontinuing antiretroviral therapy for 3 months from June 1997 produced no benefit, and in September of that year HAART was recommenced with didanosine, saquinavir and zidovudine.

During the latter part of 1997 oral thalidomide and a variety of topical agents (see Table 1) were tried without success.

Intravenous foscarnet was administered again for 2 weeks in December 1997, and resulted in the healing of one erosion and the reduction in size of a second.

The patient was not prepared to continue further with intravenous foscarnet, and was therefore treated with topical foscarnet 1%. Despite several more weeks of treatment his lesions worsened. From February 1998 1% cidofovir cream was administered topically. Healing continued gradually over many weeks and was complete by June 1998, when his CD4 count was 230 per mm³ and

his HIV viral load was below detection (Roche polymerase chain reaction (PCR) assay). In September 1998 he developed chronic HSV ulcer of the oral mucosa which was still present at the time of writing.

Case 2

A 31-year-old HIV-1 positive man with AIDS presented in March 1997 with painless penile and perianal erosions. AIDS had been diagnosed in 1994 when he developed *Mycobacterium avium* complex. Triple anti-retroviral therapy with stavudine, lamivudine and zidovudine was commenced in February 1997, when his CD4 lymphocyte count was 26 per mm³. By the time that the lesions developed his CD4 count had risen to 86 per mm³. As in case 1, the penile lesions were covered with a dense slough, but confined to the shaft of the penis. HSV was cultured from the erosions, but treatment with intravenous foscarnet for 2 weeks failed to produce any appreciable benefit, despite a confirmed sensitivity on viral resistance assays (see Table 2).

Biopsy revealed superficial erosions covered in slough. Within the eroded epithelium many cells showed the cytopathic effects of HSV infection [5], and were positive on immunohistochemistry for HSV types 1 and 2. Staining for CMV was negative. A further problem in the perianal area was that the adjacent epithelium showed severe dysplasia associated with wart virus changes amounting to anal intraepithelial neoplasia (AIN) 2/3.

Table 2 Case 2 summary

1994	AIDS (MAC) <i>Primary episode HSV</i> Commenced aciclovir prophylaxis	
1996 April	Aciclovir resistant penile and perianal HSV i.v. foscarnet 1 week: complete response	
1997 February	Aciclovir-resistant HSV i.v. foscarnet 1 week: complete response <i>Commenced HAART</i>	IC ₅₀ aciclovir >40 µM foscarnet 190 µM
1997 March	<i>Unusual HSV lesions</i> i.v. foscarnet 2 weeks: no response	CD4 count 26 per mm ³ April: IC ₅₀ foscarnet 65 µM (penile isolate) 157 µM (perianal isolate) CD4 count 86 per mm ³
1997 August	Trimovate and potassium permanganate for 4 weeks: no response	CD4 count 146 per mm ³
1997 September	Topical foscarnet: partial response	
1997 October	i.v. foscarnet for 6 weeks: complete healing of penile lesions, persistence of perianal lesions	IC ₅₀ foscarnet 80 µM (penile isolate) >400 µM (perianal isolate); CD4 count 250 per mm ³ HIV viral load below detection
1997 December	Topical cidofovir commenced: marked improvement of perianal lesions after 3 weeks	
1998 May	Small perianal lesion persisting	

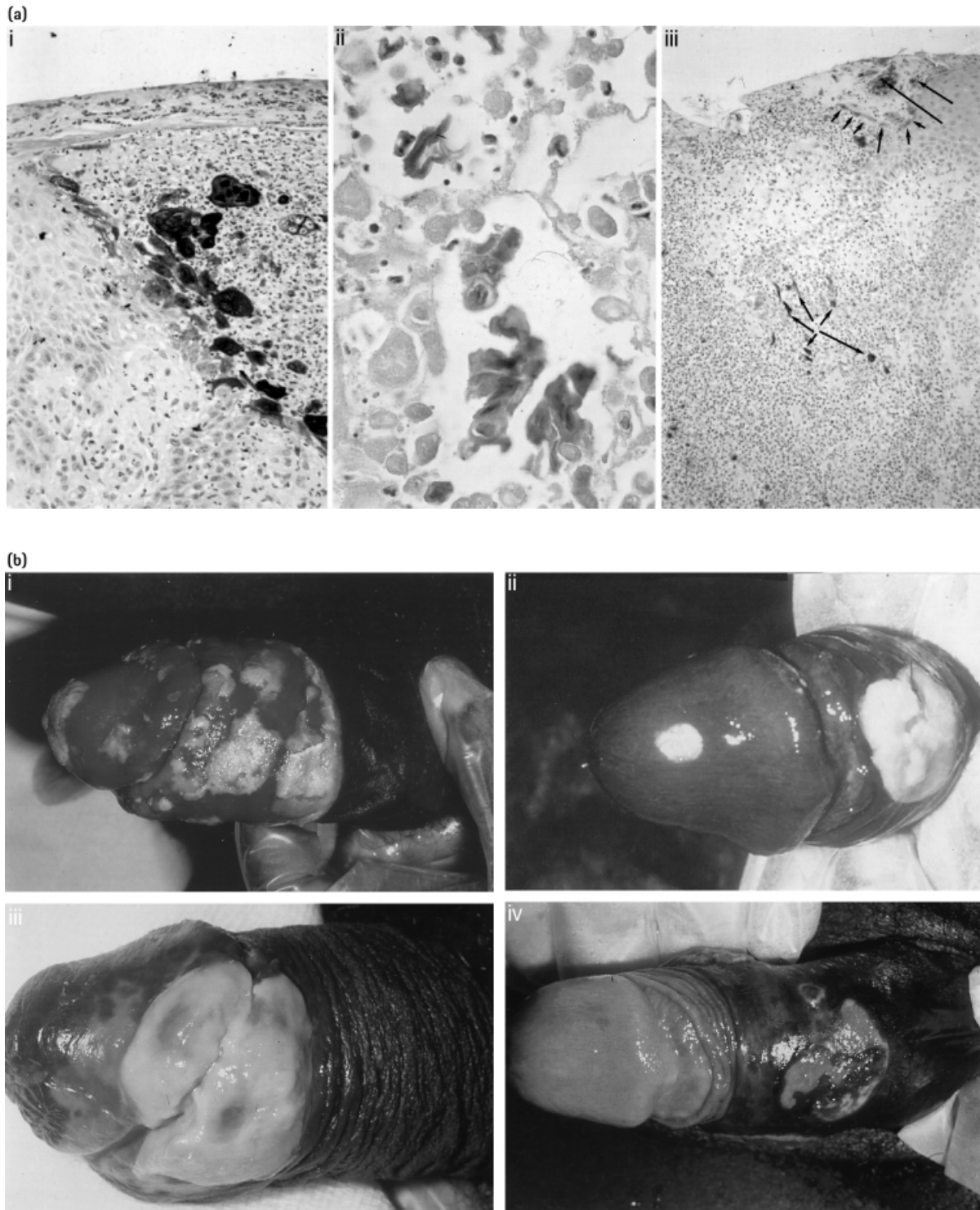


Fig. 1 (a) Biopsy specimen from case 3 taken 2 weeks after onset of symptoms. (i) High-power view of the darkly staining HSV⁺ cells in the surface epithelium adjacent to the ulcer. (ii) High-power view showing the typical cytopathic effect of HSV in the epithelium adjacent to the erosion: cells are aggregated together with cellular moulding and ground-glass appearance of the nuclei. (iii) Showing the erosion with an associated deep chronic inflammatory cell infiltrate. Dark staining (arrowed) represents HSV⁺ cells which are seen both in the surface and the deep epithelium. (b) Photographs of the characteristic lesions of chronic erosive penile HSV. (i) Case 1; (ii) case 3; (iii) case 1; (iv) case 2.

After the failure of antiviral therapy, oral azithromycin and itraconazole and topical trimovate cream were tried; all proved ineffective. He was therefore admitted in October 1997 for intravenous foscarnet. After 6 weeks of treatment the penile erosions had completely healed. Viral resistance assays showed that penile isolates remained sensitive to the drug (see Table 2), and in this context the time taken for healing to occur was quite exceptional. The perianal isolates had become foscarnet resistant and these lesions persisted, with continual production of slough and serous exudate. The only antiviral agent to which the HSV remained sensitive in the perianal region was cidofovir. When administered topically the cidofovir stopped the oozing and the excessive granulation. A recurrence of erosions on the penis in January 1998 was found to be completely sensitive to all the antiviral agents, a phenomenon which has been described previously [6]. The perianal erosions became progressively smaller using topical cidofovir, and by May 1998 the area of erosion was very small. Small erosions continue to appear and require prolonged treatment with topical cidofovir.

The immune reconstitution on HAART in this patient was dramatic. CD4 count rose to 146 cells per mm³ in June 1997 and 250 cells per mm³ in October, with an HIV viral load which was below detection on the Royal Free assay (less than 200 copies per ml).

This case differs from the first in that aciclovir resistance was detected a year before the onset of persistent HSV lesions. It should be noted that two aciclovir-resistant recurrences in 1996, and one in February 1997, were treated successfully with intravenous foscarnet for 1 week. Moreover, there was no reduction in the sensitivity of the viral isolates to foscarnet between 1996 and April 1997, and it is clear that the lack of clinical response which occurred in March 1996 following commencement of HAART was not due to emerging resistance.

Case 3

A 45-year-old HIV-1 positive man presented in November 1997 with a 1-week history of painful, weeping erosion under the prepuce. AIDS was diagnosed in 1995 following an episode of cryptococcosis, for which he was still taking fluconazole prophylaxis. Treatment with stavudine, lamivudine and indinavir was commenced 6 months previously. No sexual contact occurred in the 8 months prior to presentation. There was a history of primary genital HSV in 1994, and prophylactic aciclovir 400 mg b.i.d. was commenced in 1996 in response to minor recurrences. This prophylaxis was completely effective during the 18 months prior to presentation. The CD4 count in November 1997

was 202 cells per mm³, but had been only 26 per mm³ in June 1997.

As both syphilis serology and HSV culture were negative, the lesion was biopsied (Fig. 1). This revealed the same distinctive appearances which were seen in the first two cases (see Histopathology). Staining for HSV was positive.

Despite oral valaciclovir 1 g t.i.d. the erosions multiplied. The patient was reluctant to be admitted to hospital, but in early January 1998 he consented to 10 days of intravenous foscarnet. This resulted in complete resolution of an erosion on the shaft, but subpreputial erosions persisted. Topical foscarnet 1% was prescribed, but a phimosis developed which interfered with the efficiency of topical administration. Circumcision in May 1998 was followed by topical treatment with 1% cidofovir. The erosions improved markedly after only 2 days of treatment, after which the patient was unable to tolerate the cream. In August 1998 he was commenced on 0.3% cidofovir cream, and this resulted in complete healing after continuous use for 6 weeks (see Table 3).

At no time, despite repeated attempts, was it possible to detect HSV in swabs taken from the erosions. It could not therefore be determined whether any resistance to aciclovir was present.

Methods

Histopathology

All biopsies were fixed in 10% buffered formalin, processed to paraffin wax, cut at 3–4 microns and stained with haematoxylin and eosin, Grocott, periodic-acid Schiff, Giemsa, Gram, Warthin–Starry and Ziehl–Neelsen. Biopsies were further stained by avidin–biotin complex immunohistochemistry using monoclonal antibodies to CMV (Dako) and polyclonal antibodies to HSV 1 and 2 (Biogenesis), all of which have both cytoplasmic and nuclear targets.

HSV drug susceptibility assay (see Tables 1–3)

Plaque reduction assays were performed as described by Collins *et al.* [7] Approximately 100 plaque-forming units of HSV were inoculated onto Vero cells, and then overlaid with a semisolid medium containing varying concentrations of aciclovir and foscarnet. After 3 days cells were stained and plaques counted. The control viruses SC16 and DM21 were assayed in each run. The 50% inhibitory concentration (IC₅₀) values were then determined. The cut-off IC₅₀ was 40 µM for aciclovir resistance and 400 µM for foscarnet resistance.

Table 3 Case 3 summary

1994	Primary HSV	
1995	AIDS (Cryptococcosis)1996 Recurrent HSV Commenced aciclovir prophylaxis	
1997 May	Commenced HAART	CD4 count 26 per mm ³
1997 November	Unusual HSV lesion Oral aciclovir then valaciclovir for 4 weeks: no response	CD4 count 202 per mm ³ HIV viral load 42 178 copies per ml (Roche)
1998 January	i.v. foscarnet 10 days: partial response, then topical foscarnet 1%: no response Circumcision.	CD4 count 245 per mm ³
1998 May	Topical cidofovir 1%: unable to tolerate	CD4 count 309 per mm ³
1998 August	Topical cidofovir 0.3% for 6 weeks: complete healing of lesions	CD4 count 393 per mm ³ . HIV viral load 60 214 copies per ml (Chiron)
1998 December	New lesions	CD4 count 358 per mm ³ HIV viral load 157120 copies per ml (Chiron)

Tissue typing: HLA class I and II alleles

Genomic DNA was extracted from EDTA blood using a Puregene DNA isolation kit. The DNA was tested by PCR-SSP using a 144 phototype reaction panel which identifies specificities at HLA-A, -B, -C, DRB-1, DRB-3, DRB-4, DRB-5 and DQB-1 loci, as has been described previously [8].

In vitro lymphocyte functional activity

Blood samples were collected from case 1 in April 1998, from case 2 in July 1998 and from case 3 in May 1998. Peripheral blood mononuclear cells (PBMCs) in autologous plasma were stimulated with T and B lymphocyte mitogens and a panel of antigens, including HSV, to determine if there was a functional lymphocyte defect which could account for the clinical presentation. Three different mitogens were used: phytohaemagglutinin A (PHA), concanavalin A (Con-A) and pokeweed mitogen (PWM). PHA and Con-A induce proliferation of CD3⁺ T cells, while Con-A preferentially stimulates CD8 T cells, at least in rats, although in humans this distinction is not so clear [9]. PWM induces T-cell-dependent proliferation of B lymphocytes. The panel of antigens consisted of a mixed pool of irradiated PBMCs from healthy donors as a source of alloantigens, and antigenic extracts from *Candida albicans*, *Mycobacterium tuberculosis* purified protein derivative (PPD), tetanus toxoid, measles and HSV. Lymphocyte functional activity was determined by measuring proliferative responses following 3 days of stimulation with mitogen and 6 days with antigen. Proliferation was assessed by [³H]-thymidine incorporation by cells in the S-phase of the cell cycle. [³H]-thymidine was added for the last 6 h of culture and the results expressed as

cell-associated radioactivity as counts per minute (c.p.m.).

Results

Histopathology (Fig. 1)

In all three cases the inflammatory response seen in the biopsies was similar: above the erosion an inflammatory slough; at the base of the erosion vascularized granulation tissue with some infiltration by neutrophils; underlying the erosion a striking dense chronic inflammatory infiltrate, predominantly of plasma cells (which did not show any light chain restriction by immunocytochemical staining) and eosinophils, with scattered lymphocytes and histiocytes. The prominence of plasma cells and eosinophils was an unusual feature which has not been described previously [10]. Immunohistochemistry showed the presence of HSV-infected epithelial cells at the margins of the erosions and to a lesser extent in the deep epithelium.

Tissue typing: HLA class I and II alleles (Table 4)

It is striking that all individuals shared the class I molecules HLA B72 and HLA Cw0202 and the class II allele DRB-4. HLA B72 is relatively common in African populations; only 0.9% of Caucasian British individuals carry the marker.

In vitro lymphocyte functional activity (Table 5)

Each case showed a different pattern of impaired lymphoproliferative responses, as might be expected of patients with an AIDS diagnosis. The HSV-specific lymphoproliferative

Table 4 HLA class I & II alleles

Case 1	A2	B4901	B72	Cw0202 0701	DRB-3 DRB-4	DOB02	DOB0603
Case 2	A2301, A30	B4201	B72	Cw0202 1701	DRB-4	DOB02	DOB03
Case 3	A0302 A7401	B4901	B72	Cw0202 0701	DRB-4	DOB05	DOB0302

Table 5 (a) Mitogen-dependent lymphoproliferative responses and (b): antigen-dependent lymphoproliferative responses, both expressed as counts per minute, with control (TCM)

(a) Mitogen	TCM	PHA	Con-A	PWM			
Reference range [8] (c.p.m.)	<1000	>12000	>10000	>8000			
Case 1	242	9325	1643	3070			
Case 2	273	47803	32672	20230			
Case 3	746	63139	58541	46541			

(b) Antigen	TCM	Allo	Candida	PPD	Tetanus	Measles	Herpes
Reference range [8] (c.p.m.)	<1000	>8000	>4500	>8000	>6000	>4500	>4500
Case 1	522	39410	7838	42171	3985	1968	8106
Case 2	150	4689	1850	1669	134	156	1619
Case 3	657	42348	1208	70199	1118	5807	17029

ferative responses were normal in cases 1 and 3 and present but subnormal in case 2.

Discussion

The important features of these similar cases are that: three heterosexual Ugandan males with an AIDS diagnosis were commenced on the same triple antiretroviral therapy regime of stavudine, lamivudine and indinavir. In each case the regime was highly effective in raising CD4 lymphocyte counts. All had a history of genital HSV, for which two were taking prophylactic aciclovir. After a variable length of time on HAART, ranging from 4 weeks to 6 months, each developed florid genital erosions, associated with the production of copious epithelial slough and serous exudate.

The histology of the lesions was the same in each case, with evidence of the presence of HSV on immunohistochemistry. There was a failure of lesions to respond to antiviral therapy of dosage and duration which resulted in complete resolution prior to the commencement of HAART, and this could not be accounted for in terms of increased antiviral resistance. It is reported that the median time to complete healing of aciclovir-resistant HSV lesions using intravenous foscarnet is only 6 days [3,11].

We believe this to be a previously unreported adverse consequence of HAART, the result of partial immune restoration, reminiscent of the recently described syndrome of immune recovery vitritis [12]. Immune recovery vitritis is a syndrome of resurgent inflammation in the retina in patients with inactive CMV retinitis who have been commenced on HAART. Systemic steroids have shown some efficacy in treating the condition [12]. An increase in the incidence of herpes zoster has also been reported to occur shortly after commencing HAART [13]. Severe anogenital HSV has been reported in two Australian patients following HAART, in an Aboriginal woman and in a Caucasian male who developed haemorrhagic lesions [14]. The pathological mechanism in these cases, which responded readily to conventional therapy, is likely to be different from that which continues to affect our patients. The only clear link between the two groups is the antecedent HIV immunosuppression followed by a degree of immune restoration.

Cell-mediated immunity to HSV is largely a function of natural killer (NK) cells, macrophages, CD4 and CD8 lymphocytes [15]. Lymphoproliferative responses are usually markedly impaired in AIDS. Ongoing immunological investigation of patients commencing HAART at the Chelsea & Westminster Hospital has shown restoration of

many responses, including those to HSV, after 4 weeks of treatment. There was a similar 4 to 6 weeks time interval between commencement of HAART and onset of pathology in two of our cases. After more than a year of HAART, however, case 2 still had impaired HSV specific lymphoproliferative responses.

We postulate that following commencement of HAART there was a partial restoration of immunity to HSV which was sufficient to heighten immune responsiveness without being adequate to clear the infection, resulting in a hypersensitivity-type response. The absence of cultivable HSV in case 3 is in keeping with this hypothesis. We cannot explain satisfactorily why treatment with moderately potent topical steroids was not beneficial in cases 1 and 2. It was not considered that oral corticosteroids would confer an additional advantage over topical in such well circumscribed and superficial lesions.

It is noteworthy that no cases of chronic erosive HSV of the penis following HAART have been detected in Caucasians, despite the fact that most of our patients belong to this ethnic group. This raises the possibility of an immunogenetic link. Known links between HLA and immunity to HSV include the dependence of NK lysis of HSV infected cells on a HLA DR⁺ accessory cell population [16], and the inhibition of the same by HLA-B and HLA-C [17]. A large proportion of T lymphocytes infiltrating HSV lesions express DR antigens, as do the affected epithelial cells, on which the expression of DR antigens may increase during infection [7]. All our cases shared common HLA-B, C and DR alleles, but exactly how these might interact to give rise to abnormal immunity to HSV remains to be determined.

We recommend prolonged intravenous foscarnet followed by topical cidofovir (the latter we made by taking a 1% solution left over from intravenous administration, diluting if necessary to 0.3%, and mixing it with unguentum Merck) in the management of similar cases. A placebo-controlled trial of topical cidofovir for aciclovir-resistant cutaneous HSV infection has shown that a concentration of 0.3% is as effective as 1%, with complete healing in 30% of patients in a median time of 21 days [18]. Early circumcision may facilitate therapy when there is involvement of the glans or prepuce.

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