Recalcitrant Pseudotumoral Anogenital Herpes Simplex Virus Type 2 in HIV-Infected Patients: Evidence for Predominant B-Lymphoplasmocytic Infiltration and Immunomodulators as Effective Therapeutic Strategy

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Background. In patients with human immunodeficiency virus (HIV) infection, genital herpetic lesions may be extensive and tend to persist for longer periods; in addition, atypical hypertrophic, ulcerative, or pseudotumor forms have been reported, frequently showing resistance to acyclovir (ACV) treatment.

Methods. Between 2003 and 2011, 10 HIV-1–infected patients presenting with chronic pseudotumoral anogenital herpes simplex type 2 (HSV-2) infections were studied.

Results. All patients developed chronic, hypertrophic HSV-2 anogenital lesions with multilesional presentation in 7 cases and involvement of 2 anatomical sites in 6 of them. At the time of diagnosis, the median $CD3^+CD4^+$ absolute blood count was 480.5 cells/μL (range, 165–632 cells/μL), whereas the plasma HIV load was undetectable in all cases. Histopathologic analysis of lesion biopsies showed a moderately dense dermal polytypic plasma cell infiltrate. Detection of HSV-2 by culture and/or polymerase chain reaction was positive for all patients, with evidence for ACV-resistant strains in 6 of 8 cases. In addition, viral resistance to ACV was found only in HSV-2 isolated from ulcerative lesions, whereas purely pseudotumoral ones harbored sensitive strains. Durable control was observed with HSV DNA polymerase inhibitors in only 2 cases, and the immunomodulators imiquimod and thalidomide allowed 5 patients to reach sustained complete response.

Conclusions. HSV-2–related pseudolymphoma in HIV-infected patients is characterized by a predominant polyclonal lymphoplasmacytic infiltration, and is frequently refractory to antiherpetic drugs. Immunomodulatory therapeutic strategies using thalidomide showed consistent efficacy, and should be considered early during the course of disease.

Keywords. human immunodeficiency virus; AIDS; HIV; pseudotumoral anogenital herpes; acyclovir-resistant HSV infection.

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Herpes simplex virus type 2 (HSV-2) is the primary causative agent of genital ulcerations [1, 2]. The standard treatment for symptomatic primary and recurrent genital herpes relies on acyclovir (ACV) and related nucleoside analogues [3]. In patients with human immunodeficiency virus (HIV) infection, herpetic lesions can be extensive and tend to persist for longer periods and/or with more frequent recurrences; in addition, atypical

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clinical presentations may be observed [4–6]. Indeed vegetative, hypertrophic, ulcerative, or pseudotumoral features have been reported, often leading to misdiagnosis [7–32]. These rare pseudotumoral forms of anogenital HSV-2 may mimic epidermoid carcinoma or lymphoma, and the reported cases have emphasized the poor response to treatment with ACV [21, 31]. Although these treatment failures have been associated with the emergence of drug-resistant virus subtypes, the role of viral resistance to ACV and to other antiviral drugs such as foscarnet and cidofovir has not been established per se [33, 34]. Therefore a systematic investigation of clinicopathologic, immunologic, and virologic features of these pseudotumor lesions is required to enhance the understanding of the mechanisms underlying this disease variant and to improve its therapeutic management.

In the present work, we report 10 HIV type 1 (HIV-1)–infected patients with chronic pseudotumoral anogenital HSV-2 infections. We report their histopathologic and immunophenotypic patterns, the viral genotypic and phenotypic sensitivity profiles, and the efficacy of an immunomodulatory treatment strategy according to the likely pathogenesis of this rare syndrome.

PATIENTS AND METHODS

Study Patients

Between 2003 and 2011, we collected clinical data of 10 HIV-1–infected patients presenting with a chronic pseudotumoral anogenital HSV infection. Essential characteristics of study patients are summarized in Table 1.

Histopathologic and Immunohistochemical Studies

Eleven skin formalin-fixed, paraffin-embedded biopsies were available from all 10 study patients. In brief, 2-μm-thick sections were obtained from paraffin-embedded tissue and stained with hematoxylin and eosin. The slides were reviewed by 1 dermatopathologist (M.Bat.). Immunohistochemical analysis on paraffin-embedded material was performed with primary antibodies against the following antigens: CD3 (Dako, polyclonal, dilution 1:50), CD8 (Dako, clone 144B, 1:50), CD20 (Beckman Coulter, clone L26, 1:400), granzyme B (Dako, clone GrB7, 1:50), CD138 (Dako, clone M115, 1:50), κ light-chain (Dako, Polyclonal, 1:10 000), λ light-chain (Dako, Polyclonal, 1:20 000), HSV (Menarini, Polyclonal, prediluted), and FoxP3 (Abcam, clone 22 510, 1:50). Subsequent incubations with biotinylated secondary antibodies and then with the avidin-biotin-peroxidase complex were performed, followed by revelation using the DAB detection kit (Dako). The semiquantitative analysis of infiltrating T- and B-lymphoplasmocytic cellular subsets was estimated by M.Bat., based on in situ immunostaining analysis with respective monoclonal antibodies (anti-CD3, -CD8, -granzyme B, -CD20, -CD138, -κ, -λ immunoglobulin light chains) or quantitatively (FoxP3). HSV was identified by morphology and by immunostaining. Appropriate positive and negative controls were performed.

Table 1. Demographic Characteristics, HIV-1 History, and Immunologic and Virologic Status in 10 HIV-Infected Patients With Pseudotumoral Herpes Simplex Virus Type 2 Infection

Variable	Value
Sex, male/female, No.	6/4
Age, y, median[a] (range)	49.5 (34–70)
Race/ethnicity, No.	
White	2
Black	7
North African	1
CDC stage[a], No.	
A	1
B	1
C	8
Time between diagnosis of HIV infection and skin symptoms, y, median (range)	4.5 (0–16)
Prior antiretroviral therapy[a], No.	
None	1
HAART	9
Peripheral blood cell count, cells/μL, median[a] (range)	
Lymphocytes	2350 (1400–4040)
$CD3^+CD4^+$	480.5 (165–632)
$CD3^+CD8^+$	906.5 (520–1971)
Ratio CD4/CD8	0.5 (0.2–1.4)
HIV-1 RNA, $\log_{10}$, median (range)	Undetectable

Abbreviations: CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.

[a] At the time of diagnosis of recurrent acyclovir-resistant herpes simplex virus infection.

Molecular Analysis of Clonality

The clonality status was assessed using polymerase chain reaction (PCR) multiplex amplifications of T-cell receptor gamma (TCR-γ) and immunoglobulin H (IgH) V(D)J junctions performed on DNA extracted from skin biopsies and peripheral blood mononuclear cell samples in 2 cases, as previously described [35].

Virologic Studies

HSV isolation in cell culture was performed from genital ulceration specimens in viral transport medium. These samples were inoculated onto human fibroblast cells (MRC5). Virus typing was determined on infected-cell culture by use of monoclonal antibodies against HSV type 1 (HSV-1) and HSV-2 (Microtrak, Dade Behring, Paris, France). Between 2003 and 2005, HSV-1 and HSV-2 DNA detections were performed using commercial PCR assay (Herpes consensus generic and Hybridowell herpes identification kits, Argene-Biosoft, Varilhes, France). Since

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2005, real-time PCR assay has been used for the detection and quantification of HSV-1 and HSV-2 as described elsewhere [36].

In vitro susceptibility to ACV was assessed first by plaque reduction assay (phenotyping) and second by thymidine kinase gene sequencing (genotyping) [37]. For phenotyping, cultures were allowed to progress to complete HSV-specific cytopathic effect. Antiviral susceptibilities were determined with a chessboard titration of each virus strain, allowing simultaneous titration of the virus with various concentrations of antiviral drug and without antiviral drug. Susceptibilities to acyclovir (Glaxo Wellcome, Greenford, UK) and foscarnet (Astra Pharmaceutical Products, Westboro, Massachusetts) were done on Vero cells (African Green monkey kidney cells). Susceptibility to antivirals was assessed by the calculation of the concentration of the drug causing a 50% inhibition of viral replication (IC_{50}). Cutoff values for antiviral resistance were 6.5 μM for acyclovir and 400 μM for foscarnet. For genotyping, thymidine kinase gene was amplified and sequenced as previously described [38]. Amplified products were sequenced using an ABI 3100 Genetic Analyzer (Applied Biosystems). Contigs were assembled and ambiguities resolved by manual review of chromatograms, and alignments were done using Geneious 5.0 (Biomatters, Auckland, New Zealand).

Immunologic Studies

Lymphocyte populations were analyzed in fresh whole blood EDTA samples by direct 3- or 4-color immunofluorescence with a FacsCalibur analyzer (Becton Dickinson, San Jose, California). The percentages and absolute values of main lymphocyte subset T cells were determined using the following antibodies: CD45-PerCP, CD3-FITC, CD4-APC, CD8-PE or -PerCP, DR-PE, and CD38-PE from Becton Dickinson.

Evaluation of Response Under Treatment

A complete response was defined as the resolution of all clinical skin lesions. Partial response was defined as reduction of at least 50% in the surface of lesions. Less than 50% regression of lesions and stability or progression were considered to be lack of response to therapy.

RESULTS

Ten HIV-1–infected patients presenting with a chronic pseudotumoral anogenital herpes simplex infection, 6 men and 4 women with a mean age of 49.5 years (range, 37–70), were recorded between 2003 and 2011. Characteristics of study patients are summarized in Table 1. Patients developed HSV anogenital lesions within a median time of 4.5 years (range, 0–16) after the first diagnosis of HIV infection, and the delay of onset of lesions after the start of highly active antiretroviral therapy (HAART) ranged from 1 month to 2 years. Painful pseudotumoral lesions were consistent findings in all patients, with multilesional (2–6) presentation in 7 patients and involvement of 2 anatomical sites in 6 of them (Figure 1*A*); 3 patients

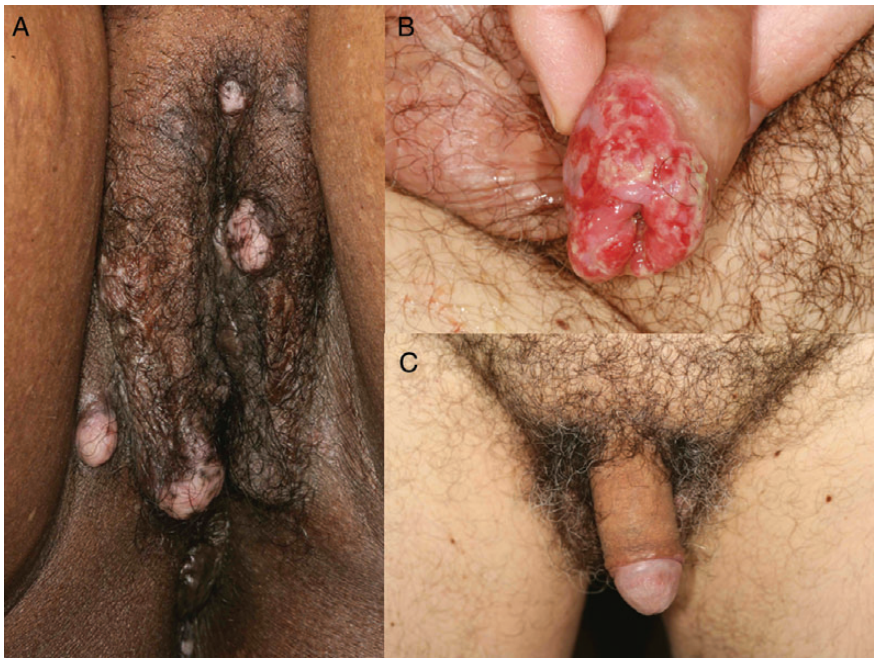

Figure 1. Clinical features and response to thalidomide. Perineal pseudotumoral herpes in a human immunodeficiency virus (HIV)–infected woman (*A*). Ulcerated pseudotumoral herpes in an HIV-infected man before (*B*) and after (*C*) 4 weeks of 100 mg thalidomide treatment daily.

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Table 2. Histopathologic and Immunophenotypic Characteristics of Pseudotumoral Herpes Simplex Virus Type 2 Infection in 10 HIV-Infected Patients

Variable	Value
Epidermal features, No.	
Hyperplasia	11/11
Ulceration	10/11
HSV cytopathic effect	7/11
HSV immunostaining	8/11
Dermal infiltrate, median (range)	
Plasma cells	80% (60–80)
κ/λ ratio	2/1 (n = 4)
	3/1 (n = 7)
B lymphocytes	10% (5–10)
T lymphocytes	10% (5–20)
Cytotoxicity, median (range)	
$CD8^+$ (% of $CD3^+$ cells)	80% (60–90)
Granzyme B (% of $CD8^+$ cells)[a]	5% (1–10)
Immunoregulation	
FoxP3, cells/mm^2[b]	0–2

Abbreviation: HIV, human immunodeficiency virus; HSV, herpes simplex virus.

[a] Granzyme B expression was restricted to focal subepidermal areas close to ulcerations.

[b] When encountered, FoxP3 cells were very rare, isolated, and subepidermal.

presented with a single lesion. Superficial ulcerations were observed in 7 patients (Figure 1*B*). A superficial, diffuse lymphadenopathy was detected in 2 patients. At the time of diagnosis, the median $CD3^+CD4^+$ and $CD3^+CD8^+$ absolute blood counts were 480.5/μL (range, 165–632) and 906.5 (range, 520–1971), respectively, whereas plasma HIV RNA was undetectable in all cases (Table 1).

Histopathologic analysis of skin biopsies (Table 2) showed a moderately dense mononuclear dermal infiltrate (Figure 2*A*), composed for its vast majority of plasma cells (80% of the infiltrate; Figure 2*B*) identified by CD138 staining analysis (Figure 2*C*), which were polytypic with a κ/λ ratio of 2. The other inflammatory cells comprised small B cells (10% of the infiltrate) and T cells (10% of the infiltrate). T cells predominantly expressed a $CD8^+$ phenotype (80% of the T-cell infiltrate; Table 2). Granzyme B was expressed by few subepidermal cytotoxic lymphocytes close to the ulceration; Foxp3 was either not expressed or limited to rare isolated subepidermal lymphocytes. Epidermal hyperplasia and ulceration were often present, and dermal fibrosis and regular vascular hyperplasia were constant features. Presence of HSV infection was assessed in 7 samples based on morphologic cellular changes (Figure 2*D*), and ascertained in 8 biopsies by immunohistochemistry, often focally. In the last 2 patients, HSV was not identified in situ, although detection of HSV-2 by culture or PCR was positive.

PCR analysis of Vγ-Jγ rearrangements of TCR and IgH in skin biopsies (Supplementary Figure 1) revealed a polyclonal pattern in the 2 cases analyzed.

Detection of HSV-2 by either culture or PCR was positive for all patients. One to 33 isolates were available per patient. Of 8 patients who underwent HSV-2 genotypic and/or phenotypic testing, 6 had evidence for ACV-resistant strains at least once, although sensitive strains were also detected in 4 of them at different times during follow-up. In addition, viral resistance to ACV was found only in HSV-2 isolated from ulcerative lesions, whereas purely pseudotumoral ones harbored sensitive strains. According to HSV thymidine kinase sequence analysis, ACV resistance was related to deficient thymidine kinase in 3 of 3 available cases (C or G insertion/deletion in homopolymer repeats leading to either a frameshift or stop codon; Table 3).

The response to treatment was evaluated in 9 patients, as the 10th patient was lost to follow-up (Figure 3, Table 4). All 9 patients received ACV or valacyclovir treatment without efficacy in 8 cases. Two patients underwent surgery with a relapse after a few months for 1 patient and a complete response during 12 months' follow-up for the other. Six patients received multiple 2- to 3-week courses of intravenous foscarnet infusions combined with topical cidofovir (n = 4), or topical cidofovir only (n = 2) for several weeks. All patients experienced a progressive improvement of skin symptoms, with stable complete response over a 15-month follow-up in 1 case, and partial response under treatment in 5 other patients, followed by relapse occurring a few months after the end of treatment in all of them (Table 3). Treatment with topical imiquimod 5% cream was initiated in 3 patients from this latter group and in 1 patient from the ACV/valacyclovir group, at the dosage of 3 times weekly, with an overall good safety and sustained complete response in 1 patient (Table 3). However, this was a short-duration complete response requiring a therapeutic change. Thalidomide 100–200 mg a day was started in 4 patients following failure/relapse of imiquimod [4] and of foscarnet/cidofovir [1], respectively. In all cases, a rapid (<1 month), dramatic regression of mucocutaneous lesions leading to sustained complete response was observed under thalidomide treatment (Figures 1*C* and 3). Two of 4 patients (numbers 2 and 4) still underwent thalidomide treatment 100 mg a day without side effects (complete response duration of 13 months). One patient (number 1) discontinued thalidomide 100 mg/day after 9 months for personal convenience and did not report any side effects. He was still in complete response 4 months after stopping thalidomide. The last patient (number 7) began thalidomide at 200 mg daily. The dose was decreased to 100 mg a day because of headaches and digestive disorders. Finally, the patient stopped the treatment after 8 months because of the side effects and was lost to follow-up.

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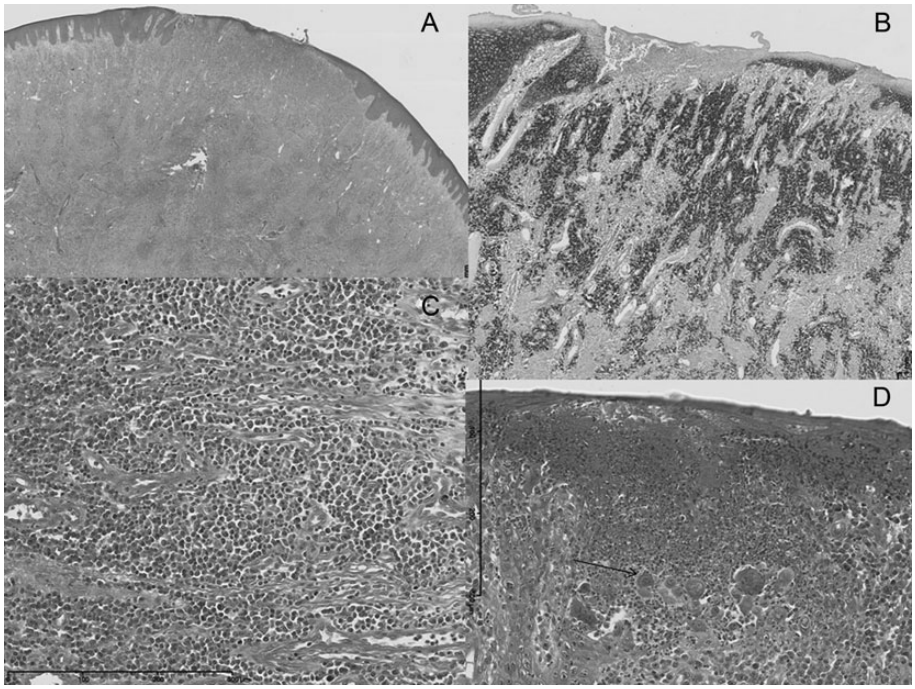

Figure 2. Histologic sections of lesional skin. *A* and *B*, Ulcerated skin sections stained with hematoxylin and eosin, showing a dense dermal infiltration by a majority of plasma cells confirmed by a specific immunostaining with anti-CD138 antibody (*C*). Magnification ×1.25 (*A*) and ×20 (*B*). Lesions strongly suggestive of herpes simplex virus infection such as formation of syncytia and nuclear inclusion body (arrow) were seen (*D*, magnification ×40).

Overall, sustained healing was observed with surgery in 1 case, HSV DNA polymerase inhibitors in 2 cases, and immunomodulators (imiquimod or thalidomide) in 5 cases.

DISCUSSION

In the present work, we analyzed 10 HIV-1–infected patients presenting with a chronic pseudotumoral anogenital herpes simplex infection. The clinical findings observed in these patients, for example, hypertrophic anogenital lesions, confirmed the previous observations [7–32].

The exophytic clinical presentations of HSV-2 infection may raise diagnostic difficulties in HIV-infected patients, mainly the discrimination between neoplasia and infection. Moreover, the sensitivity of various diagnostic tests can be affected by the reactive changes present in these lesions [39]. Likewise, it may be necessary to repeat both HSV isolates (cultures and PCR) and biopsies in cases suspicious for HSV. Virologic results obtained from mucocutaneous samples were always positive in our patients and were helpful for diagnosis. One of the new insights from the present study is the predominance of polyclonal lymphoplasmocytic B cells among the cellular lesional infiltrate.

Table 3. Thymidine Kinase Sequence Mutations Over Time for 3 Available Cases

Patient	Date	Sample	Resistance Profile	Resistance Mutation	Unknown Mutation	Polymorphism Mutations
7	Feb 2009	Vulva	S	0		G39E N78D L140F
	Jan 2011	Vagina	S	0		G39E N78D L140F
	Oct 2011	Buttock	Unknown		L313S	G39E N78D L140F
	Nov 2011	Pubis	R	Insertion of 1G codon 145		G39E N78D L140F
	Nov 2011	Buttock	Unknown		L313S	G39E N78D L140F
6	Nov 2010	Anus	R	Insertion of 1C codon 196		G39E N78D L140F
4	Jan 2011	Penis	R	Insertion of 2G codon 145		G39E N78D L140F
	Jan 2011	Scrotum	S	0		G39E N78D L140F
	Jan 2011	Penis	R	Insertion of 2G codon 145		G39E N78D L140F
	Jan 2011	Scrotum	S	0		G39E N78D L140F

Abbreviations: R, resistant; S, sensitive.

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Table 4. Follow-up Treatment in Study Patients

Patient	Pseudotumoral Lesions	Ulcerated Lesions	No. of Isolates per Patient	At Least 1 In Vitro Testing of the HSV-2 Strain ACV Resistant	Surgery	Antiviral Treatment Response (Response Duration)[a]	Immunomodulator Treatment Response (Response Duration)[a]
1	Yes	No	7	Yes	No	ACV/valacyclovir: lack of response Foscarnet: PR Topical cidofovir: lack of response	Imiquimod 5%: CR (2 mo) Thalidomide: CR (13 mo)
2	Yes	Yes	6	No	Yes Relapse	ACV/valacyclovir: lack of response Topical cidofovir: PR	Thalidomide: CR (13 mo)
3	Yes	No	3	NA	No	ACV/valacyclovir: lack of response	Imiquimod 5%: CR (10 mo)
4	Yes	Yes	25	Yes	No	ACV/valacyclovir: lack of response Foscarnet: PR	Imiquimod 5%: CR (2 mo) Thalidomide: CR (13 mo)
5	Yes	Yes	13	Yes	Yes, CR (12 mo)	ACV/valacyclovir: lack of response Foscarnet: PR Topical cidofovir: PR	Imiquimod 5%: intolerance
6	Yes	Yes	13	Yes	No	ACV/valacyclovir: lack of response Foscarnet: PR Topical cidofovir: PR	No
7	Yes	Yes	33	Yes	No	ACV/valacyclovir: lack of response Foscarnet: PR Topical cidofovir: PR	Imiquimod 5%: PR Thalidomide: CR (8 mo)
8	Yes	Yes	4	NA	No	ACV/valacyclovir: CR (6 mo)	No
10	Yes	Yes	10	Yes	No	ACV/valacyclovir: lack of response Topical cidofovir CR (15 mo)	No

Abbreviations: ACV, acyclovir; CR, complete response; HSV-2, herpes simplex virus type 2; PR, partial response; NA, not available.

[a] Response duration when there is a complete response.

Although the antigen specificity of this B-cell component remains to be elucidated, the presence of a polyclonal identical pattern in all the different samples, as assessed by both anti-κ/λ light-chain immunostaining analysis and spectra typing analysis of IgH V(D)J rearrangements, supports the hypothesis of a dysregulated antigen-driven immune reaction, likely to be directed toward HSV-2 derived antigens. The lack of cytonuclear abnormalities and of a dominant clonal component is also supportive for the pseudolymphoma nature of this entity. Despite a significant delay exceeding 1 year in most patients, one may raise the hypothesis of a clinical consequence of an immune reconstitution, as previously reported [40]. Another consistent feature in patients with this rare syndrome is the lack of opportunistic infection, to be related to their preserved immunologic status. Together with the scarce contribution of T cells to the lesional mononuclear infiltrate, these latter findings plead for the hypothesis that a restricted functional defect of HSV-2-specific T cells, and not a broad immunodeficiency, underlies the pathogenesis of this syndrome. This latter model is reinforced by results from studies of virologic sensitivity to antiherpetic drugs. Indeed, there was no clear correlation with the presence of sensitive HSV-2 strains and a clinical response to ACV, and complete response to valacyclovir, topical cidofovir, or even intravenous foscarnet was very unusual or transient in our patients, confirming previous observations [21, 31]. Indeed, ACV-sensitive strains have been identified in ACV-refractory pseudotumoral lesions contemporary to ACV-resistant strains identified in ulcerative lesions. In addition, other antiviral treatments failed in

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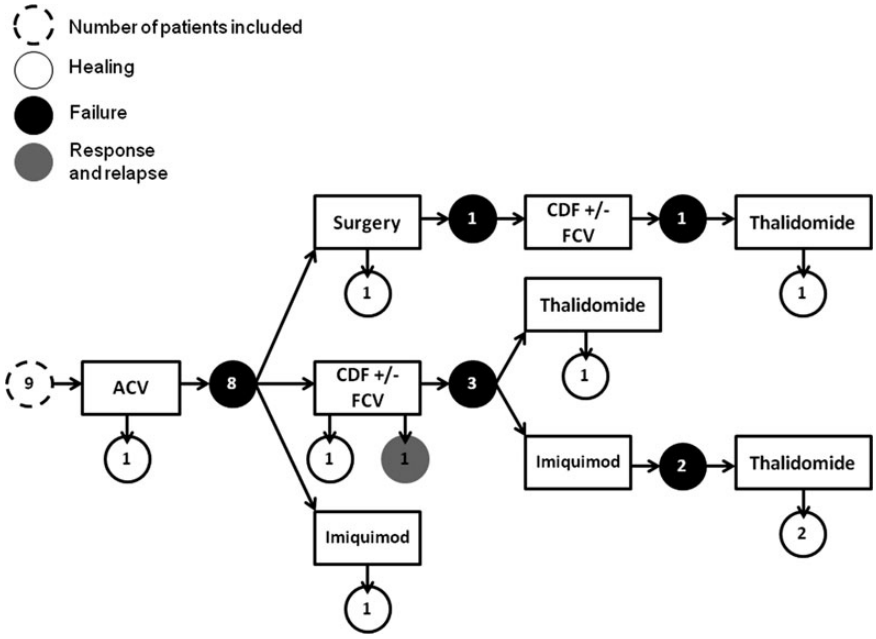

Figure 3. Therapeutic strategy for the 9 patients and response under different treatments (surgery, herpes simplex virus DNA polymerase inhibitors, and immunomodulators). The numbers in circles refer to the number of patients with the corresponding outcome as indicated by the color of the circle. One patient (gray circle) was lost to follow-up after 2 lines of treatment. Abbreviations: ACV, acyclovir; CDV, cidofovir; FCV, Foscavir.

other cases to cure the lesions. Finally, the lack of resistance mutant selection despite prolonged ACV exposure in ulcerated lesions suggests that HSV-2 subtypes were not under antiviral pressure and that a virologic resistance to antiherpetic drugs is unlikely to play a major role in the pathogenesis of this pseudolymphoma. The observation of ACV-resistant strains in ulcerative lesions and ACV-sensitive strains in pseudotumoral lesions supports the hypothesis of reduced or absent drug delivery to pseudotumor tissue. This hypothesis would deserve further studies using ACV concentration measurement in lesional tissues.

The results of treatment efficacy are also in keeping with the pseudolymphoma nature of the syndrome. Indeed, although topical foscarnet and cidofovir may show transient efficacy in a few cases refractory to AVC [18, 30–31], they had only partial activity in our experience, whereas the immunomodulatory drugs such as imiquimod and thalidomide, used alone or sequentially, were consistently effective. The clinical response following topical imiquimod, a Toll-like receptor 7 agonist that boosts both innate and adaptive antiviral immunity, provide support that an immune stimulus targeting innate immunity may overcome the deficiency of antiherpetic immunity that persists despite HAART-induced immune recovery in these patients. In our experience, imiquimod led to a short-duration response with an early relapse after treatment was stopped. On the other hand, the striking efficacy of thalidomide in all 4 patients from the present series who received this regimen is in agreement with the former observation by Verberkmoes et al [41]. Taking into consideration the efficacy of thalidomide in B-cell lymphoplasmocytic disorders such as multiple myeloma or other types of B-cell cutaneous pseudolymphomas [42], it would be of interest to prospectively investigate the efficacy and safety of this drug in HSV-2 pseudolymphoma in HIV-infected patients.

In conclusion, despite the benefit of DNA polymerase inhibitors to cure ulcerative lesions, immunomodulatory and antiproliferative strategies should be considered early to treat HSV-2–positive pseudotumoral lesions.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. H. B. has consulted for and received payment for lectures from Abbott, Amgen, Boehringer, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, and Pfizer and has received grants from Pfizer. J.-M. C. has consulted for Novartis and has received payment for lectures from BMS, Novartis, and Cepheid. G. C. has received payment for lectures from MSD and Gilead. M. Bat. has received payment for manuscript preparation from Leo. J. M. J. has received payment for lectures from

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Uriage. J. M. M has received payment for lectures from Gilead, grants from Merck, and travel expenses from Abbott, and serves on the boards of MSD, BMS, and Janssen. J. L. has received payment for lectures from Abbott Molecular. E. S. has received payment for lectures from Abbott. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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