Laboratory Diagnosis of Herpesvirus Infections in Patients with Pemphigus Vulgaris Lesions

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Key Words

Pemphigus vulgaris · Herpesviruses · Viral diagnosis · Herpes simplex virus · Cytomegalovirus · Human herpesvirus type 6 · Human herpesvirus type 7

Abstract

Background/Aims: Pemphigus vulgaris (PV) is an autoimmune disorder that has an etiology impacted by genetic and exogenous factors. Viral infections, in particular herpesvirus infections, have been identified as possible PV triggers which in addition cause serious complications in these patients. This study investigates the frequency of herpesvirus infections in patients with PV lesions. **Methods:** Polymerase chain reaction and DNA sequence analyses were used to determine the presence of herpes simplex virus (HSV)-1/2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus types 6, 7, and 8 (HHV-6, HHV-7, and HHV-8) DNA in 105 mucosal and/or skin swabs harvested from 23 patients presenting with PV lesions. **Results:** Thirty-six samples collected from 17 patients were positive for at least 1 virus; 3 were positive for HSV-1, 2 for HSV-2, 2 for CMV, and 7 each for HHV-6 and HHV-7. Coinfections were observed in 15 samples. Infections with VZV, EBV, HHV-6A, and HHV-8 were not detected. Herpesvirus infec-

tions were detected in 21% (13/62) of reactivated lesions, 54.5% (18/33) in persistent lesions, 40% (2/5) in exacerbated lesions, and 60% (3/5) in lesions in remission. **Conclusion:** PV lesions which do not show improvement following administration of adequate immunosuppressive therapy should be screened for the presence of herpesvirus infections.

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Introduction

Pemphigus vulgaris (PV) is an autoimmune disorder characterized by blistering and ulceration of the mucous membranes, the skin (or both), loss of normal epithelial cell-to-cell adhesion (acantholysis), and the presence of circulating autoantibodies directed against desmoglein 3 (and in some cases desmoglein 1) [1, 2]. Progression and exacerbation of pemphigus are the result of interactions between endogenous (genetic) and exogenous factors such as drugs (particularly those containing thiol and phenol and calcium channel blockers), physical insults such as burns, ultraviolet radiation, X-rays, infections, neoplasms, hormones and pregnancy, nutritional factors, emotional stress, and vaccination [1].

The first report of a possible association between viruses and PV was published in 1974 [2]. Since then, several case reports have pointed to the possible association between viral infections (in particular herpesvirus infections) and PV progression and severity [2–15]. To investigate the frequency of herpesvirus infections in patients with PV, we used polymerase chain reaction (PCR) to determine the presence of viral DNA from swabs taken from mucosal and/or skin lesions from patients with PV.

Materials and Methods

Patients

Patients ($n = 23$; 22–61 years of age) who had previously been diagnosed with PV were enrolled in the present study. They attended the Department of Stomatology of the Dentistry University of the Federal University of Rio de Janeiro or were hospitalized in the Department of Dermatology of the Hospital Universitário Clementino Fraga Filho and the Hospital Universitário Pedro Ernesto between March 2007 and September 2010. All patients voluntarily gave consent to participate in this study and the study protocol was approved by the Ethics Committee of the Hospital Universitário Clementino Fraga Filho of the Federal University of Rio de Janeiro.

Respective lesions were defined as either reactivated, exacerbated, persistent, or in remission. Reactivated lesions were defined as lesions that had previously not been present but developed as a consequence of the nonhealing profile of the disease. Exacerbated lesions were defined as preexisting lesions that worsened. Persistent lesions were defined as lesions that despite corticosteroid treatment did not heal, and lesions in remission were defined as healing lesions.

DNA Extraction

Mucosal and/or skin samples were collected from lesions using a swab stored in viral transport media. If the patient presented with multiple lesions, swabs were taken from each lesion separately. In addition, examinations were repeated for all patients who were hospitalized more than once. Nucleic acids were extracted from 200 μ l of sample using a Wizard® Genomic DNA Purification Kit (Promega, Madison, Wisc., USA) according to the manufacturer's recommendations.

Polymerase Chain Reaction

Specimens were analyzed by conventional PCR assays as previously described for the detection of herpes simplex virus (HSV) types 1/2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus types 6, 7, and 8 (HHV-6, HHV-7, and HHV-8) [8, 9, 16, 17]. Positive and negative controls were used in all reactions. PCR products were observed on ethidium bromide-stained agarose gels.

To confirm the specificity of the PCR products and to differentiate HSV-1 and HSV-2, amplified DNA from positive samples were purified using the Wizard SV gel and the PCR Clean-Up System Kit (Promega), and the sequences determined using the Big-Dye® Terminator Cycle Sequencing Kit and the ABI PRISM® 3100

automated DNA sequencer (Applied Biosystems, Foster City, Calif., USA). DNA sequences were edited using the Chromas software (Technelysium Pty Ltd, Australia) and compared to the DNA sequences available in the GenBank® (www.ncbi.nlm.nih.gov) using the BLAST tool (www.ncbi.nlm.nih.gov/BLAST).

Results

We examined 15 female (65%) and 8 male (35%) patients with a mean age of 45.5 years, ranging from 23 to 61 years. Eleven patients identified themselves as Caucasian (47.8%; 11/23), followed by Mulattos (34.8%; 8/23) and Blacks (17.4%; 4/23). Ten patients (43.5%) presented with mucocutaneous lesions, 9 (39.1%) only with mucosal lesions, and 4 patients (17.4%) presented only with cutaneous lesions. No patients reported a previous history of herpetic lesions, and all were already receiving immunosuppressive treatment. No significant differences were observed between anatomic sites regarding the presence of specific herpesviruses.

Samples ($n = 105$) were collected and analyzed from the 23 patients. Herpesviruses were detected in 36 samples collected from 17 patients. The positivity of the samples in relation to the virus type which was detected and the collection site is described in table 1. Six patients tested negative for all herpesviruses.

Sixty-two lesions were classified as reactivated, 33 as persistent, and 5 each as in remission and exacerbated. Of these, viral infections were detected in 21% (13/62) of reactivated lesions, 54.5% (18/33) in persistent lesions, 40% (2/5) in exacerbated lesions, and 60% (3/5) in lesions in remission.

HSV-1 was detected as a single infection in 3 cases and in mixed infections in 3 separate cases. In contrast, HSV-2 was found only in single infections. CMV was detected in 3 cases. In patient 13 CMV was detected in 2 samples from different sites on separate occasions. HHV-6B was the most commonly detected virus, and mixed HHV-6B infections were identified in 7 cases. The most frequent coinfections identified were HHV-6B/HHV-7. Finally, HHV-7 was found in 6 cases. VZV, EBV, HHV-6A, and HHV-8 were not identified in any samples examined (table 1).

Patient 14, a 63-year-old male who had been diagnosed with PV in 2003, presented with skin and oral lesions. PV was initially controlled with oral prednisone; however, during treatment he experienced hypertension, femur aseptic necrosis, exacerbation, and recurrence of the disease. His treatment was, therefore, supplemented with azathioprine and cyclophosphamide, resulting in re-

Table 1. Characteristics of the patients and clinical specimens analyzed

Pa-tient	Sex	Age years	Race	Date of collection	Type of sample (number of samples)	Type of lesion	Virus detected (site of collection/number of positive samples)
1	f	59	C	04/24/2007 06/12/2007 11/30/2007 08/01/2008	ML (1)/SL (1) ML (1)/SL (1) ML (2)/SL (1) ML (2)/SL (2)	reactivated reactivated reactivated reactivated	– – – –
2	m	48	C	07/20/2007 11/09/2007 02/14/2008 02/26/2010	ML (1)/SL (1) ML (1)/SL (2) ML (2) SL (1)	reactivated/persistent reactivated remission persistent	HSV-2 (nose/1) ¹ – – –
3	f	51	M	07/27/2007 11/23/2007	ML (1)/SL (2) ML (1)/SL (2)	reactivated reactivated	HHV-6B (thorax/1) –
4	f	22	M	08/16/2007	ML (1)	reactivated	HSV-1 (left vestibule/1)
5	m	36	B	10/23/2007	ML (1)	reactivated	–
6	f	48	M	10/09/2007	ML (2)	persistent	–
7	m	35 36	M	11/01/2007 08/29/2008	ML (2) ML (3)	exacerbated reactivated	HSV-1/HHV-6B/HHV-7 (tongue/1) HHV-6B (jugal mucosa/1); HHV-6B/HHV-7 (tongue/1)
8	f	46	C	11/06/2007	ML (3)	reactivated	–
9	f	49 51	M	01/11/2008 04/09/2010	ML (2)/SL (1) SL (3)	reactivated exacerbated	HHV-7 (thigh/1) HHV-6B (shin/1)
10	m	33	B	02/29/2008	ML (1)/SL (3)	reactivated	HHV-6B/HHV-7 (left shoulder/1)
11	f	47	M	03/25/2008 08/31/2010	ML (2)/SL (2) ML (3)	reactivated reactivated	HHV-7 (neck/1) –
12	f	52	C	05/06/2008	SL (3)	reactivated	HSV-1/HHV-7 (right ear/1); HSV-1/HHV-6B/HHV-7 (neck/1); HHV-6B/HHV-7 (abdomen/1)
13	f	50	C	05/15/2008 05/15/2008 06/25/2009 08/06/2009 08/13/2009 09/16/2009	SL (1) ML (1) SL (1) SL (4) SL (2) ML (1)/SL (3)	reactivated reactivated persistent reactivated persistent persistent	HHV-6B (thorax/1) CMV/HHV-6B (jugal mucosa/1) CMV (right superior eyelid/1) – HSV-1 (right superior eyelid/1) HHV-7 (right superior eyelid/1)
14	m	61	C	12/04/2008	ML (3)	persistent	HSV-1/HHV-7 (lip; left and right border of the tongue/3)
15	m	23	C	03/14/2009 05/07/2009	SL (2) SL (2)	reactivated reactivated	– –
16	f	59 60	M	05/26/2009 12/01/2009	ML (3) ML (3)	persistent persistent	HHV-7 (floor of the mouth/1) HSV-2 (right jugal mucosa/1); CMV/HHV-7 (left jugal mucosa/1); HHV-7 (tongue/1)
17	f	29	B	05/29/2009	ML (1)	persistent	HSV-1 (left jugal mucosa/1)
18	m	48	C	07/10/2009	SL (2) ML (1)	remission remission	CMV (left shoulder/1); HHV-6B (abdomen/1) HHV-7 (left jugal mucosa/1)
19	f	57	C	08/06/2009	ML (2)	persistent	HHV-6B (right jugal mucosa/1)
20	f	54	M	10/22/2009	SL (1)	persistent	HHV-6B/HHV-7 (left superior eyelid/1)
21	m	49	C	12/04/2009	SL (3)	reactivated	HHV-6B/HHV-7 (axil/1)
22	f	33	B	03/02/2010 05/28/2010 09/30/2010	ML (3)/SL (1) ML (2) ML (3)	persistent persistent persistent	HHV-6B (vagina/1); HHV-6B/HHV-7 (lip and tongue/2); HHV-7 (left jugal mucosa/1) – –
23	f	47	C	09/16/2010	ML (1)/SL (2)	reactivated	–

SL = Skin lesion; ML = mucosal lesion; C = Caucasian; B = Black; M = Mulatto.

¹ Only the persistent lesion was positive.

mission and control of all skin lesions (with only mild improvement of the oral lesions). Analysis of the samples collected from the oral lesions identified an HSV-1 and HHV-7 coinfection that was successfully treated with acyclovir (10 mg/kg IV and then 800 mg PO 5×/day). Pulse therapy was suspended and prednisone administration was gradually tapered without any relapses [13]. The fact that the lesion healed after acyclovir administration suggested a primary role of the HSV-1 in the condition of the patient since this drug does not seem to be effective against HHV-7 infections.

Patient 13 was another interesting case: a 50-year-old, hypertensive, diabetic female who was amaurotic as a consequence of bilateral posterior subcapsular cataracts due to corticosteroid therapy and with a clinical and histopathological diagnosis of PV (in 2005) that was controlled with the administration of prednisone (20 mg/day) and cyclophosphamide pulses every 21 days. During the follow-up, she presented with an HSV infection on the erythematous base of the eyelid (top and bottom right) and was treated with oral acyclovir. One month later, she developed acute exacerbation of PV. The patient was then hospitalized, and the dose of prednisone was increased to 1 mg/kg/day (60 mg/day) with dexamethasone pulses every 21 days in addition to maintaining cyclophosphamide pulses every 21 days. After 40 days, reepithelialization of the lesions was observed, but an ulcerated area of about 2 cm at the right upper eyelid with no signs of healing remained. Swabs were taken from this patient and analyzed for herpesvirus DNA. The first sample collected on June 25, 2009 was CMV positive; however, because there were no clinical signs of active CMV infection, the attendant physician decided not to treat her with gancyclovir. Since the lesion persisted for 2 months, other samples were collected on August 13, 2009, and at the following examination they tested positive for HSV-1. The patient was then treated with acyclovir (400 mg PO 5×/day and then 800 mg 2×/day), and the lesion subsequently healed [14].

Discussion

The possible association between herpesviruses and PV has been the subject of several studies; however, it still remains unclear what role the herpesviruses play in the progression and presentation of PV. Some studies were unable to identify associations between viral infections and pemphigus [18–21]. Conversely, other studies suggested that herpesviruses could trigger PV progression [2,

3, 7–9]. In addition, other studies have suggested that herpesvirus infections represented a complication of pemphigus resulting from immunosuppressive therapies and/or a causative factor associated with treatment-resistant lesions [6, 10, 12–17, 22–26].

The most common viral infections reported in pemphigus patients are caused by herpesviruses, particularly HSV [6, 10–12, 15, 23–26, 28–30]. HSV infections are often identified in association with recurrent/persistent PV lesions in patients already undergoing corticosteroid treatment. In most cases, HSV diagnosis was delayed for several months, because viral lesions mimicked PV lesions [12, 22, 25, 26]. However, when the HSV diagnosis was established and the treatment was initiated, the lesions cleared promptly. In this study, reactivated, persistent, and/or exacerbated lesions caused by HSV-1 and/or HSV-2 infections were treated with acyclovir resulting in lesion clearance [13, 14].

Infections caused by other herpesviruses such as CMV, VZV, EBV, or HHV-8 have also been described in association with PV patients [5, 7, 8, 15, 24, 27, 31–34]. CMV has been detected mostly in association with persistent lesions [20, 29]. In contrast to treatment regimens described for HSV infections, the use of antiviral treatment of CMV infections in pemphigus patients is controversial [14, 15].

Few studies have reported the occurrence of HHV-6/7 infections in pemphigus patients. Tufano et al. [7] identified HHV-6 DNA in peripheral blood mononuclear cells of 3 patients with PV and in 1 patient with pemphigus erythematosus, and Takahashi et al. [35] described a case of a patient with pemphigus foliaceus that developed a drug-induced hypersensitivity syndrome during prednisolone treatment. The antibody profile of this patient suggested reactivation of infections with HHV-6, CMV, and EBV, suggesting that the transient suppression of both cellular and humoral immunity may have triggered viral reactivation. In our study, HHV-6B and HHV-7 were the most common viruses found (7 and 6 cases, respectively). Whether these viruses actually played a role in the perpetuation, reactivation, or exacerbation of pemphigus lesions is difficult to establish based on the data obtained, because there is no antiviral therapy available to treat infections caused by these viruses at this time. Consequently, a clinical relationship between the presence of these viruses and PV was difficult to establish. However, it is worth noting that cases 13, 14, 16, 19, 20, and 22 presented with persistent lesions and were also positive for these viruses. In these cases, an increase in corticosteroid doses could be detrimental to the patients.

In this study, mixed infections were identified in 15 samples: 7 each in reactivated and persistent lesions and 1 in an exacerbated lesion. HHV-6 and/or HHV-7 were present in all coinfections in association with HSV-1 or CMV. The consequences of such interactions are not clear. It has been described, however, that HHV-6 could be reactivated from latency after coinfection with HHV-7 [36], and CMV disease is frequently associated with concurrent HHV-6 and HHV-7 reactivation in transplant patients [37, 38]. Moreover, HHV-6 is capable of pronounced interactions in vitro with CMV and human immunodeficiency virus resulting in the induction of immunosuppression and apoptosis [39], suggesting that these coinfections could have aggravated lesion progression and/or delayed the healing process.

Clinically, it might be difficult or even impossible to identify herpetic infections in PV patients [10, 12–15, 22–26, 30]. Persistent concomitant herpetic coinfections

should be considered in the context of PV lesions that need to be confirmed by laboratory tests, particularly since herpesvirus infections are often present in PV lesions. These observations suggested that modifications to current PV treatment regimens include treatment with antivirals to target herpesvirus infections in particular. In addition, increasing or changing immune suppression treatments for presumed refractory pemphigus will not improve disease presentation [10, 13–15, 23–26, 30].

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