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Cutaneous lumbosacral Herpes Simplex virus among patients hospitalized for an advanced disease

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Abstract
Background Cutaneous Herpes simplex virus (HSV) infections are regularly observed in lumbosacral areas, and many are refractory to appropriate initial diagnosis and management.
Objective We aimed to evaluate the incidence of lumbosacral HSV among advanced disease patients, to estimate their survival index from HSV onset, and to describe their clinical and virological characteristics.
Methods A prospective, descriptive study was conducted in a palliative and continuous care centre, collecting patients with suspected cutaneous HSV lesions in the lumbosacral area.
Results From 2008 to 2010, 24 patients were included: 19 had HSV-2 confirmed by at least one laboratory test. Incidence of HSV-2 was 2.67% (1.73–4.33%, 95% CI). No age, gender or survival differences were observed compared to the global population in the centre. Most lesions were detected early as vesicles (14/24) or small ulcers. Sensitivity was good for all diagnostic methods (62.5% for immunofluorescence and 79.2% for culture and/or PCR). Outcome was favourable under classical antiviral drugs and topical antiseptic dressing.
Conclusions Cutaneous lumbosacral HSV remains uncommon in patients hospitalized with advanced diseases. Most of these patients suffer from pressure ulcers or other dermatitis; we advocate increased attention of this diagnosis to avoid skin complications and added pain.

Conflict of interest
The authors declare no conflict of interest.

Funding sources
No funding was obtained for this work.

Introduction
Mucocutaneous herpes simplex viruses (HSV) are well described in immunocompetent young adults.1–3 Two sub-types exist. Sub-type 1 (HSV-1) is most frequently found on the oral mucosa and other localizations above the waist, mainly cephalic; and HSV-2, more frequently found on genital and other localizations below-the-waist.4 Once the virus has infected the neural ganglia of the posterior roots of the spinal cord, recurrences of the infection occur with various triggering factors, including general immune host-related as well as environmental factors.

HSV-2 genital recurrences are mostly benign, but are of particular importance among adults because of the risk of sexual contamination or transmission during childbirth. In other circumstances, frequent recurrences may be highly debilitating,5 and therapeutic and/or prophylactic follow-up is necessary. Extranodal and extensive manifestations of mucocutaneous herpes are well described in immunosuppressed patients.6–9 Quick and efficient management is essential to limit the risk of becoming chronic, or of superficial or deep dissemination, particularly neurologically. In all these situations, diagnostic procedures and appropriate management have been proposed and internationally validated.9 However, cutaneous herpetic recurrences seem to be less common with advancing age, and data are lacking in the literature concerning the very fragile population of patients in palliative and continuous care centres.

In palliative medicine, herpetic lesions are regularly observed on the buttocks, perianal and sacro-coccygeal regions. Among bedridden or chair-bound patients, these infectious herpetic lesions can often be confused with other infections frequently observed in these pressure-bearing areas. Erosive dermatitis of the buttocks
due to maceration, candida infection and pressure ulcers are the most common co-morbidities. The occurrence of cutaneous herpes in situations of friction and permanent pressure is not well described.10,11

In our department, we used to manage these superficial ulcers and regularly confirm herpetic lesions.12 Therefore, we aimed to study the prevalence of lumbosacral cutaneous HSV, the associated risk factors and evolution in a population with a very low mobility and life expectancy in a palliative care setting.

Methods

Study design
Descriptive, prospective, single-centre study.

Patient population
The study protocol was approved by the institutional clinical research ethics committee of the Geneva University Hospitals, in accordance with the international guidelines for Good Clinical Practice Guidelines outlined in the Declaration of Helsinki. Written informed consent from each patient or from their designated surrogate were obtained before enrolment, as soon as the suspected lesion was detected. The study concerned the patients hospitalized in palliative and continuous care of Geneva University hospital (1901 beds). This department has 104 beds, 600 admissions per year, and is located 10 km from the laboratories and acute care departments of the University hospital. The admission criteria are determined by the patient health condition, mainly a very low life expectancy with difficult to manage symptoms and difficulties to be kept at home. Cases were any patients presenting with suspected cutaneous herpes lesions (grouped vesicles, acute and painful superficial ulcer) below the waist observed between April 2008 and May 2010. All patients hospitalized in the palliative and continuous care department during the study period were eligible for inclusion. The control population was the whole population hospitalized in the department during the study period, calculated with the number of admissions and discharges (death or alive). The only exclusion criterion was refusal to participate in the study.

Patient characteristics were collected at baseline, namely: age, gender, main disease that was the indication for hospitalization (including cancer and presence of metastasis), use of immunosuppressive treatment over the previous 6 months (e.g. chemotherapy, radiotherapy, steroids), nutritional status and albuminemia.

The primary objective was to evaluate the incidence of mucocutaneous lumbosacral HSV infection among palliative care patients and their prognostic survival index from onset. Secondary objectives were to evaluate associated risk factors, to improve the clinical diagnosis; to evaluate our laboratories diagnosis; to optimize the palliative care management by advocating targeted analgesic treatment focused on the cause, rather than on global pain.

Clinical procedures
During a preliminary phase, all the physicians and nurses working in the palliative care department underwent teaching about cutaneous herpes infections and possible confusion with dermatitis or grade 1–2 pressure sores.12 A nurse specialized in wound care and a senior physician in palliative care worked closely with the dermatologist. Potentially eligible patients were prospectively registered and the general characteristics and description of their cutaneous lumbosacral lesion were recorded, namely: history of any previous herpetic infection, localization of the lesion; lesion description (vesicle or ulcer; date of appearance of the lesion, local evolution of the lesion by means of photographs: J0, J2, J7, J15; date of healing; date of recurrence). Local treatment for herpes or any other cause of ulcer was provided and followed up by the dermatologist and specialized nurse. Treatment comprised disinfectant povidone iodine applications and drying of oozing lesions. An absorbent and easy-to-remove protective dressing was applied once or twice daily. Appropriate positioning of the patient in the bed or chair by the occupational therapist in case of emerging pressure sores was encouraged. The treating physician was free to prescribe systemic antiviral treatment. Oral valacyclovir or intravenous acyclovir was proposed for the purposes of the study. The dose and duration of treatment was similar to those recommended in immunocompetent patients with recurrent genital HSV, namely: oral valacyclovir 500 mg × 2/day or intravenous acyclovir 5 mg/kg/8 h for 5–10 days, as soon as laboratory confirmation of herpes was obtained. Treatment tolerance and herpetic evolution under treatment were recorded, particularly any cutaneous extension of lesions, simultaneous general condition worsening, fever and new neurological symptoms.

Technical procedures

Sampling and transportation
A good standardized quality of sampling and transportation was obtained by the investigators and already tested in the previous training months. The suspected herpetic lesion was scraped with a scalpel and applied to a slide. Fixation was done immediately by freezing at −20 °C in the freezer compartment of the refrigerator that can be found easily in any care unit. Any sampling was sent to the dermatology and virology departments by the usual shuttle transportation. The procedure had to be the same as the one usually used for clinical follow-up to promote and facilitate such cutaneous management after the study.

Laboratory tests
Three different tests were systematically used to diagnose each herpetic mucocutaneous lesion. Identification of HSV antigen was by direct immunofluorescence (DIF). The slide was fixed with acetone and monoclonal antibodies specific for, respectively, HSV-1, HSV-2 and varicella zona virus (VZV) were conjugated with fluorescein isothiocyanate (FITC) and added to the four slide areas (one for HSV1, one for HSV2, one for VZV,
Clinical herpetic lesions were confirmed by direct immunofluorescence (DIF) (15 of 24 samples) and by PCR in 19 of 24. Fourteen of 24 patients were suspected of having herpes infection by clinical presentation and virological tests were performed in all of them.

**Statistical analysis**
Data are presented as mean ± SD for quantitative variables, and number (%) for qualitative variables. Incidence rates were computed with their 95% Poisson confidence interval. Fischer exact test was used to compare gender proportion. Survival curves are presented according to the Kaplan–Meier method and comparison between cases and population of the department was performed using the log rank test. All statistics were performed using STATA statistical software: Release 11.1 (Stata Corp, College Station, TX, USA).

**Results**
During the study period, 712 patients were discharged (dead or alive) from our department. Among these, 29 had a high suspicion of lumbosacral herpes type 2. Informed consent could not be obtained from two of them and three died before inclusion was possible. Thus, 24 patients were included and analysed, corresponding to a virology-confirmed incidence rate of 3.37% (2.16–5.02%, 95% CI). Laboratory tests confirmed the presence of herpes virus in 19 subjects, corresponding to a virology-confirmed incidence rate of 2.67% (1.73–4.33%, 95% CI). Patient characteristics are presented in Table 1. Figure 1 shows an example of herpetic lumbosacral lesions in two study cases. Mean age was 72.4 ± 11.8 years old (range: 49.7–94.6). Seventeen patients died during the study period (70.8%). The majority of subjects were women [17 (range: 49.7–94.6)]. Seventeen patients died during the study period (70.8%).

**Table 1** General, clinical and virological data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients: n = 24</th>
<th>Patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F</td>
<td>5/17</td>
<td>20.8/70.8</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>Metastatic</td>
<td>10</td>
<td>41.7</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Anticancer trt &lt;6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>17</td>
<td>70.8</td>
</tr>
<tr>
<td>Hormonotherapy</td>
<td>3</td>
<td>12.5</td>
</tr>
<tr>
<td>Localization of lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buttocks</td>
<td>16</td>
<td>66.7</td>
</tr>
<tr>
<td>Sacrum + fold</td>
<td>7</td>
<td>4.2</td>
</tr>
<tr>
<td>Perianal</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Type of lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vesicles</td>
<td>14</td>
<td>58.3</td>
</tr>
<tr>
<td>Ulcerations</td>
<td>10</td>
<td>41.6</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valacyclovir per os</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Povidone iodine</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>15</td>
<td>62.5</td>
</tr>
<tr>
<td>Culture and/or PCR</td>
<td>19</td>
<td>79.2</td>
</tr>
<tr>
<td>Death</td>
<td>17</td>
<td>70.8</td>
</tr>
</tbody>
</table>

Trt, treatment; DIF, direct immunofluorescence; PCR, polymerase chain reaction.

Survival time after herpes suspicion, which corresponds to the date of sampling (Fig. 2) ranged from 0.1 to 9.1 months [1.03 (2.15), median (interquartile range)] and was not significantly different than the department population discharged from our centre (P = 0.9612). Median survival was 77 days in both patients with suspected herpes infection and control population. The majority of patients included in the study had cancer as their primary diagnosis (18/24), 55% of whom were multi-metastatic. Seven patients had had chemotherapy in the 6 months preceding hospitalization and eight had had radiotherapy; four patients had had both. Seventeen patients (70.8%) were treated with dexamethasone. Nutritional status estimated in 23/24 patients by albuminemia, showed a median albuminemia at 24 g/L (range: 18–27), far from the normal albuminemia range of 35–48 g/L. Eight patients reported a previous history of below-the-waist (genital or lumbosacral) herpes. HSV was located on the buttocks in 16 cases, on the skin of the sacrum in six, in the fold of the buttocks in one and on the perianal region in one case. No genital HSV was observed during the 2-year study period. The majority of lesions were vesicles (58.3%).

DIF was positive in 15/24 patients and all isolates were HSV-2. The total result for PCR and culture was 19 confirmed HSV-2 cases (79.2%). Although systematically sought, no VZV was found on any of the 24 samples. Most of the patients underwent systemic oral treatment with valacyclovir, at the standard dose of 500 mg × 2 daily for 4–12 days. No intravenous administration...
was needed. One confirmed HSV case did not receive any systemic treatment. The five patients in whom HSV was not confirmed received only topical antiseptic care. In all cases, local care consisted of povidone iodine applied on a dry dressing and changed every day. Systemic antiviral drugs were given until complete healing of the identified lesions. The majority of the lesions healed in less than 1 week; the longest recorded healing time was 12 days. No cutaneous or neurological extensions were observed. Both local tolerance to antiseptic care and general (particularly digestive and renal) tolerance to antivirals was good.

Discussion

Incidence of lumbosacral HSV in our palliative medicine and continuous care department is low and comparable to the results found in patients suffering from cancer and presenting oral lesions confirmed as herpes type 1.14 Posterior lumbosacral HSV recurrences remain rare in frail populations, such as patients in palliative or long-term care. Surprisingly, we did not observe any other presentations of HSV type 2, even in severely immunocompromised patients (multi-metastatic cancer recently treated by chemotherapy). The patients included in our study had a similar comorbidity profile as compared to the department’s recruitment: 75% had cancer (usual proportion of admissions to our department). It is noteworthy that 70.8% of the herpetic cases were under dexamethasone, which is frequently used as a long-term anti-inflammatory drug in end-of-life patients. Our findings confirm the results observed in another immunocompromised population, where no positive association between chronic low dose steroids and herpetic infections could be found.15 Benedetti et al. showed that 21% patients with primary genital herpes will go on to develop non-genital recurrences.16 However, both these reports did not investigate HSV occurrences over a long period of time, or in patients aged over 60. Our study population has the particularity of associating the immune risk factors, age and the probable bedridden risk factor as described by Nikkels and Mackay.10,11

Incidence of lumbosacral herpes in palliative care settings has never been studied. We report only the first description of such cutaneous infections and the role of supine position for this localization, as too many factors are combined in our patients. Hospitalization stress and local mechanical stimulation have been also suggested to play a role in respiratory HSV-1 recurrences in critical care patients.17 In this study, Bruynseels et al. showed that the presence of herpes is an unfavourable prognostic risk factor for patients in critical care. In another study, HSV-1 shedding was associated with reduced survival in patients under assisted ventilation.18

Macerated dermatitis, candida infections and grade 1, 2 pressure sores are the most common lesions seen in the posterior lower body area. Management of such skin dermatosis is integrated into
systematic training of carers working in long-term and palliative settings. In these institutions, dermatologists work as consultants and cannot see all the acute or benign skin diseases. Medical training targets nutritional and mobility deficiencies and pressure ulcers. Early detection of patients at risk of pressure ulcers and of low grade pressure ulcers remains the main goal in the majority of health policies. In this way, we wish to optimize the clinical attention in a particularly fragile population and encourage general physicians to ask for specialized advices. With the help of this study, we trained physicians to broaden their differential diagnosis, we also raised awareness among nursing staff as regards better wound management: before the study we used to see extensive herpetic cases mixed to pressure ulcers and now observe that patients are earlier diagnosed and managed. Cutaneous herpetic recurrence is obviously under-diagnosed in elderly and frail hospitalized populations. In 2009, the global prevalence rate of pressure ulcers (grades 1–4) in the Palliative medicine and continuous care department was 12.5%. Half of these cases were localized on the sacral or ischiatic parts of the body. We retrospectively checked that none of our herpetic skin ulcers were registered in that prevalence. Non-invasive laboratory tests are of importance to recommend. This study was also the opportunity to evaluate the performance of the different laboratory techniques used in our hospital. Sensitivity of DIF, culture and PCR correspond to the results reported in the literature for these tests. Sensitivity of DIF and culture has precisely been studied on different samples by smears or scrapings from genital, oral and other skin lesions. The best results are observed in vesicles and adequate samples with cells obtained from the base of lesions. PCR is particularly accurate (Table 1). In three cases, the virus could only be isolated by PCR. To detect herpetic skin lesions, PCR remains a very convenient tool in clinical practice. It allows trained nurses and physicians, who are in daily contact with patients to take samples and thus improve early detection, facilitating the management and healing process. The usefulness of DIF is currently questionable but may remain in routine use because of its quick results (1 h) and favourable economic profile. Sensitivity fluctuates with the clinical diagnosis accuracy, the efficiency of sample collection and the age and type of the lesion. Our study took into account all these steps: direct dermatologist interventions at the patient bedside and an experienced wound management nurse. Finally, the three laboratory tests search systematically for VZV. This virus may present as a herpetic recurrence and may be associated to HSV in a same body area. Despite their patent immunosuppression, no VZV infection was clinically suspected in any patient, four of them had a past history of cutaneous zona.

In only five patients included in the study, herpetic virus was not detected. Some herpetic cutaneous lesions may be atypical even in immunocompetent patients. In AIDS patients, they can induce deep and chronic ulcers. The virus grows deeply in the dermis and may stay latent. Histopathology may be of help for diagnosis when a suspected pressure ulcer does not heal despite proper treatment.

The main benefits to be yielded from proper management of these patients are firstly, improvement of pain from the infection lesion, and secondly, prevention of ulcer extension. Clinical therapeutic studies taking place in the end-of-life setting are difficult to perform, principally because of the bad general condition of patients and the evident bad prognosis. Patients receiving palliative care in the context of lethal disease in the short or medium term should receive targeted treatment, which can rapidly have a favourable effect on the cause or symptoms, thereby improving their quality of life. Antiviral treatment is based on the standard schemes proposed for muco-cutaneous herpes. Although most of the patients were immunocompromised, neither increased doses of valacyclovir nor intravenous forms were required. Moreover, a suppressive prophylaxis using long-term daily valacyclovir low dose (500 mg/day) could be discussed. However, in light of the benign presentations and good cutaneous evolution when lesions are detected early, we do not recommend it, especially considering the reduced life expectancy of our population. Local treatment consisted of povidone iodine, an antiseptic that dries the skin and needs to be removed at least every day or every time the patient is cleaned when incontinent. Occlusive dressings used in pressure ulcer treatment should be avoided. Although not a consensus, this practice seems very efficient and well tolerated in our daily practice, as also reported by others. Due to sample size and design, our study has several limitations. We could not objectively monitor local pain symptoms during the lesion’s evolution, or evaluate analgesic modification. Body mass index had to be integrated in risk factors analysis, but was available in only for half of the patients, where it presented no difference as compared to the general population.

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