SHORT REPORT

Disseminated cutaneous herpes simplex infection in a patient with Crohn's disease under azathioprine and steroids: First case report and literature review

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Abstract

Immunosuppressive treatments used in the management of Inflammatory Bowel Disease, namely steroids, thiopurines and anti-TNF α drugs, raise the risk of acquiring opportunistic infections. However, most of these infections are mild and self-limited, not requiring specific therapy or suspension of the immunosuppressors. We report a case of disseminated cutaneous herpes simplex infection in a patient with Crohn's disease under steroids and azathioprine.

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1. Introduction

The treatment of Inflammatory Bowel Disease (IBD) is associated with an increasing use of immunomodulators, being steroids, thiopurines and anti-TNFα drugs commonly prescribed. Despite a better control of the disease with these drugs, there is a higher risk of infection and, concerning viral agents, benign infections may become severe or disseminated. We report the case of a young female with double immunosuppression (corticosteroids and
azathioprine) due to Crohn’s disease, who developed a disseminated Herpes Simplex Virus (HSV) infection, resulting from a reactivation of latent HSV. A review of the literature regarding HSV in patients with IBD is included.

2. Case description

A 21 years old female patient was admitted with abdominal pain and diarrhoea, with 8 bowel movements per day, without rectal bleeding or fever. Blood tests were remarkable for microcytic anaemia (haemoglobin of 10.9 g/dL) and increased inflammatory markers, namely C-Reactive Protein of 87 mg/L and 13,000 × 10⁹ leukocytes per litre. Colonoscopy showed aphthous ulcers in the terminal ileum and in some areas of the transverse colon, with histology showing active chronic colitis. Entero-CT scan showed inflammatory changes in the last ileal loop with an extension of 3 cm. With these elements, a diagnosis of Crohn’s disease was made, and the patient started immunosuppression with intravenous steroids and azathioprine. She was discharged asymptomatic one week later under azathioprine (AZA) 50 mg/d and prednisolone 40 mg/d.

After 3 weeks on treatment she was readmitted with diarrhoea (4 bowel movements per day) and fever (max = 38.5 °C). Fever was interpreted in the context of a flare, and she was again treated with intravenous steroids. At day 3 of admission, her clinical status deteriorated and higher fever (max = 40 °C) was elicited with poor response to antipyretics. C-Reactive Protein ascended to 200 mg/L. Antibiotic therapy was begun empirically, with ceftriaxone and metronidazole. An abdomino-pelvic CT scan excluded the presence of intra-abdominal abscess. Hemocultures and urocultures were negative. IgG antibodies against Herpes Simplex Virus 1 (HSV1) and Cytomegalovirus (CMV) were both positive, with negativity for IgM; IgG and IgM antibodies for Epstein-Barr Virus (EBV) and HSV2 were negative.

On the 3rd day, physical examination was remarkable for papular lesions in the extensor face of both legs. During the following days of hospitalization, they spread and evolved, presenting at the 5th day papular, vesicular and pustular lesions, with different stages of evolution, in the lower and upper limbs (Figs. 1 and 2), trunk, back (Fig. 3), face and scalp, suggesting chickenpox. A swab from the vesicular cutaneous lesions looking for HSV and varicella-zoster virus (VZV) DNA was done at that time. Meanwhile, intravenous acyclovir was prescribed as the patient persisted with high-grade fever being double immunosuppressed (which was stopped at this moment) and under antibiotics. Serology showed again IgG positivity for both VZV and HSV1, consistent with the previous infection with these two viruses. The swab became positive for HSV1-DNA and negative for VZV-DNA. A diagnosis of disseminated cutaneous herpes virus infection in the context of double immunosuppression (corticosteroids and azathioprine) was established. There were no mucosal lesions in the lips, mouth or genitals.

The patient became afebrile after the second day of acyclovir and she was treated for 14 days: the first seven days intravenously, followed by oral therapy.
3. Discussion

We present an atypical case of disseminated cutaneous herpes infection in a patient with Crohn’s disease under low-dose of azathioprine and steroids, requiring the suspension of immunosuppressants and the prescription of antivirals against HSV-1. This virus is transmitted by close contact, and primary infections are usually acquired during childhood and adolescence, whereas infection with HSV-2 is responsible for most genital herpes, being mostly sexually transmitted. After the first exposure, HSV becomes latent in neural cells, and nearly 90% of the adult population has serological markers of previous contact. While these viruses are normally localized in the skin or mucosa of the lips and genitals, with immunosuppressive therapy or in critical ill patients other organs may be affected, being oesophagus the most common gastrointestinal location.

HSV does not seem to be responsible for the aetiology or flares of CD. An experimental study that searched for a vast group of pathogens in colonic mucosa by PCR-based methodologies did not find this virus in any patient with this disease.3 On the other hand, in UC, super-infections with HSV, with a putative role in the origin of a flare (or, at least, favouring a poorer outcome), were reported.4

Patients with IBD may have a higher prevalence of opportunistic or severe infections, due to the immunosuppressive therapy that is increasingly applied. This risk is higher with cumulative therapies,5 malnutrition, surgery and, probably, by an immunological derangement inherent to the disease.6,7 In a recent Japanese prospective study, 9.1% of 570 patients with IBD developed opportunistic infections, particularly on those older than 50 years-old and taking azathioprine; HSV and VZV were the main agents observed but, and in contrast to what we showed, all HSV infections were limited to one location (mainly face and genitals).

It is important to highlight that HSV-related disease, even in immunocompromised patients, is normally subclinical or very mild, not warranting either discontinuation of therapy or systemic antivirals. The vast majority of cases of clinical herpes infection in patients with IBD are very limited and benign,5,6,8–13 as can be analysed in Table 1. Nevertheless, serious events as herpes hepatitis and encephalitis in patients with IBD are also reported, almost all in patients under steroids, with a high rate of mortality14–18 – Table 2.

Concerning the drugs that our patient was exposed to, azathioprine was found to raise the risk of benign herpes flares independently of steroids or infliximab, in a prospective study in patients with IBD,8 but it is important to stress that the median time between the initiation of azathioprine and such flares was 76 months. In contrast, in our patient the clinical onset was severe and azathioprine was prescribed only for 3 weeks (and in a suboptimal dose, about 1 mg/kg of body weight per day), which is not enough to even reach its maximum immunosupressant activity and therefore it may have little contribution for the development of this infection. The reason why azathioprine may contribute to HSV reactivation is not clear, but this drug promotes an immunological derangement in Natural killer cells and CD4 and CD8 lymphocytes, which is known to be crucial in preventing viral infections. Regarding steroids, the literature about its use in IBD and viral infections is very scarce,19 and the true risk of these agents is very difficult to assess, since it is almost always associated with other maintenance immunomodulators.

### Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of publication</th>
<th>Cases of IBD</th>
<th>Cases of HSV disease</th>
<th>Drugs at the time of HSV disease</th>
<th>HSV type</th>
<th>Primary vs reactivation</th>
<th>Type of infection</th>
<th>Age/Gender</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torunier et al.</td>
<td>Observational</td>
<td>18</td>
<td>1</td>
<td>Thiopurines (5), steroids (2), none (2)</td>
<td>NR</td>
<td>NR</td>
<td>Oesophagus, extremities, face</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Naganuma et al.</td>
<td>Prospective</td>
<td>29</td>
<td>1</td>
<td>Azathioprine (14); more than one immunosuppressors (18)</td>
<td>NR</td>
<td>NR</td>
<td>Face (26), genitals (2), extremities (1)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Seksik et al.</td>
<td>Prospective</td>
<td>NR</td>
<td>1</td>
<td>Adalimumab, others</td>
<td>NR</td>
<td>NR</td>
<td>Genital and skin</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Baumgart et al.</td>
<td>Prospective</td>
<td>1</td>
<td>1</td>
<td>Infliximab</td>
<td>NR</td>
<td>NR</td>
<td>Peri-anal vesicles</td>
<td>31/F</td>
<td>NR</td>
</tr>
<tr>
<td>Lopez-Negre et al.</td>
<td>Case report</td>
<td>1</td>
<td>1</td>
<td>Infliximab</td>
<td>NR</td>
<td>NR</td>
<td>Limited cutaneous</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schreiber et al.</td>
<td>RCT</td>
<td>3</td>
<td>1</td>
<td>Certolizumab (2), placebo + other (1)</td>
<td>NR</td>
<td>NR</td>
<td>Limited, location not specified</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sandborn et al.</td>
<td>RCT</td>
<td>5</td>
<td>1</td>
<td>Certolizumab (4), placebo plus other (1)</td>
<td>NR</td>
<td>NR</td>
<td>Limited, location not specified</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schaudone et al.</td>
<td>Case report</td>
<td>1</td>
<td>1</td>
<td>Infliximab</td>
<td>HSV-1</td>
<td>NR</td>
<td>Erythema multiforme plus vesicles in the lips</td>
<td>19/F</td>
<td>Good</td>
</tr>
</tbody>
</table>

**Note:**

IBD = Inflammatory Bowel Disease.

UC = ulcerative colitis.

CD = Crohn’s disease.

NR = not reported.
certolizumab, that describes HSV infections under biologics,\textsuperscript{9,10} in controlled Trials (RCTs), both in patients with Crohn's disease taking infliximab.\textsuperscript{11} Erythema multiforme manifestation caused by this virus, namely a HSV-related reactivation as disseminated cutaneous herpes in a patient with Crohn's disease, was not previously reported. Furthermore, it must be highlighted that our patient was young and her presentation was due to a reactivation of latent HSV, since she had history of labial herpes and positive IgG for HSV1. Additionally, she was only on AZA for 3 weeks (combined with steroids) and had a very atypical presentation: besides the disseminated infection with widespread lesions all over the body surface, she had no oral or genital involvement and the lesions were completely painless.

Our patient was treated with acyclovir, a nucleoside analogue that inhibits HSV replication by acting in the viral polymerase after uptake, that is the preferred drug for the treatment of these conditions. In an immunosuppressed patient, intravenous administration for 2 weeks is advisable.

Herein, it is showed a unique and atypical case of HSV reactivation with multiple papules and pustules as our case, particularly in a patient with Crohn's disease, was not previously reported. Furthermore, it must be highlighted that our patient was young and her presentation was due to a reactivation of latent HSV, since she had history of labial herpes and positive IgG for HSV1. Additionally, she was only on AZA for 3 weeks (combined with steroids) and had a very atypical presentation: besides the disseminated infection with widespread lesions all over the body surface, she had no oral or genital involvement and the lesions were completely painless.

One class of immunomodulators that is being increasingly used in patients with IBD is anti-TNF agents. A recent meta-analysis studied the risk of opportunistic viral infections in patients with Crohn's disease taking biological therapies.\textsuperscript{20} The authors only found two Randomized Controlled Trials (RCTs), both in patients with Crohn's disease taking certolizumab, that describe HSV infections under biologics,\textsuperscript{9,10} reporting a total of 6 patients with mild HSV disease. Overall, this meta-analysis found no significant difference in the frequency of HSV infection in patients taking biological therapies (RR = 1.67, CI = 0.46–6.12).

Besides the several cases of benign presentation similar to those found in the general population, in the literature, we can find a case report of a more exuberant dermatological manifestation caused by this virus, namely a HSV-related erythema multiforme in a patient with ulcerative colitis taking infliximab\textsuperscript{11} — Table 1. However, disseminated skin involvement with multiple papules and pustules as our case, particularly in a patient with Crohn's disease, was not previously reported. Furthermore, it must be highlighted that our patient was young and her presentation was due to a reactivation of latent HSV, since she had history of labial herpes and positive IgG for HSV1. Additionally, she was only on AZA for 3 weeks (combined with steroids) and had a very atypical presentation: besides the disseminated infection with widespread lesions all over the body surface, she had no oral or genital involvement and the lesions were completely painless.

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Herein, it is showed a unique and atypical case of HSV reactivation as disseminated cutaneous herpes in a patient with Crohn's disease under steroids, that was also taking azathioprine for 3 weeks. It is crucial to have in mind the raised risk of severe viral infections, even if the mechanism is not yet understood, and to have a high level of suspicion to detect atypical presentations, since an early diagnosis is warranted for the success of the treatment.

### Table 2 Published cases of serious herpes simplex infections in IBD patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of publication</th>
<th>IBD</th>
<th>Drugs at the time of HSV infection</th>
<th>HSV type</th>
<th>Primary reactivation</th>
<th>Type of infection</th>
<th>Age/gender</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shlien RD\textsuperscript{14}</td>
<td>Case report</td>
<td>UC</td>
<td>Prednisolone 40 mg/d (2 weeks)</td>
<td>HSV-1</td>
<td>Primary</td>
<td>Hepatitis</td>
<td>16/F</td>
<td>Dead</td>
</tr>
<tr>
<td>Seksis P\textsuperscript{15}</td>
<td>Case report</td>
<td>UC</td>
<td>Prednisone 40 mg/d (8 days)</td>
<td>HSV-1</td>
<td>Primary</td>
<td>Hepatitis</td>
<td>37/M</td>
<td>Dead</td>
</tr>
<tr>
<td>Alimohamadi SM\textsuperscript{16}</td>
<td>Case report</td>
<td>UC</td>
<td>Prednisolone 10 mg/d, AZA 75 mg/d</td>
<td>NR</td>
<td>Unknown</td>
<td>Encephalitis</td>
<td>22/F</td>
<td>Good</td>
</tr>
<tr>
<td>Robineau O\textsuperscript{17}</td>
<td>Case report</td>
<td>CD</td>
<td>Prednisone 50 mgndb, AZA 150 mg/d</td>
<td>HSV-1</td>
<td>Possible reactivation</td>
<td>Meningoencephalitis</td>
<td>28/F</td>
<td>Good</td>
</tr>
<tr>
<td>Francois-Dufresne A\textsuperscript{18}</td>
<td>Case report</td>
<td>CD</td>
<td>Prednisone 50 mgndb, AZA 150 mg/d</td>
<td>HSV-1</td>
<td>Possible reactivation</td>
<td>Pneumonia</td>
<td>44/M</td>
<td>Sequela</td>
</tr>
</tbody>
</table>

IBD — Inflammatory Bowel Disease.
UC — ulcerative colitis.
CD — Crohn's disease.
AZA — azathioprine.
NR — not reported.

### Conflict of interest

The author declares that there is no conflict of interest.

### References


