Herpes simplex keratitis in renal transplant patients

Israel Kremer, Aaron Wagner, Dan Shmuel, Alexander Yussim, Zaki Shapira

Abstract

Five out of 430 patients (1-16%) undergoing kidney transplantation developed an atypical clinical picture of herpetic dendritic keratitis within four weeks after surgery. It was manifested by multiple dendrites, located mainly in the corneal periphery or the limbus, developing in relatively uninfamed eyes. The response to acyclovir therapy was prolonged and took at least three weeks. Additionally, subepithelial infiltrates with ultimate scarring developed in all patients. Disciform keratopathy was not found. This clinical course is ascribed to the patients' immunosuppressed state.

The relatively high incidence of extraocular herpes simplex virus (HSV) infection as well as infections by other members of the herpes virus group in immunosuppressed patients has been reported in several studies. These HSV infections result from the reactivation of latent HSV infection rather than from primary HSV infection from an exogenous source. The reported rate of extraocular HSV reactivation for renal transplant patients varies widely. For example, Schooley et al. detected HSV infection in 18% of their patients, while Korsager et al. isolated this virus from 54% and Pass et al. from 66% of allograft recipients. These variable results probably depend on the category of patients studied, the frequency with which HSV isolation was attempted, different study protocols, and the fact that the immunosuppressive therapy of these patients is not alike. In addition, Greenberg et al. reported a difference between the rate of HSV isolation (46-8%) and the formation of manifest HSV lesions (31-8%), meaning that not all kidney transplant patients in whom the virus is isolated will develop the typical herpetic lesions.

In contrast to the numerous studies reported on extraocular HSV infections in renal transplant patients we found scarce information in the English literature on the clinical course and rate of HSV keratitis in these patients. Therefore the purpose of the current retrospective study was to evaluate the prevalence of dendritic herpetic keratitis and its clinical appearance in kidney transplanted patients being treated with immunosuppressive therapy.

Patients and methods

The records of all patients undergoing kidney transplantation in the Department of Organ Transplantation, Beilinson Medical Center, between the years 1980 and 1989 were reviewed independently by two of the authors. The charts of those patients affected with active herpetic dendritic keratitis were studied and the following parameters were evaluated: (a) timing of infection following transplantation; (b) previous herpetic infections; (c) clinical course of corneal herpetic disease; (d) extraocular manifestations of herpetic infection; (e) response to therapy; and (f) immunosuppressive therapy.

Results

Four hundred and thirty patients underwent kidney transplantation between the years 1980 to 1989. Five of these patients (1-16%) developed acute dendritic keratitis between 10 days and four weeks after surgery. Their ages ranged from 36 to 42 years (Table 1). All the patients were treated immediately following transplantation by triple therapy, which included prednisone 2 mg/kg, azathioprine 2-5-3-0 mg/kg, and cyclosporin-A 3-5 mg/kg. During the first month after surgery the steroid treatment was

![Schematic drawing of active dendritic keratitis in patient no. 3. Note the stromal infiltrates (arrow) and the peripheral location of most of the dendrites.](http://bjo.bmj.com/)

### Table 1 Patients' data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Timing post-transplantation</th>
<th>No. of dendrites</th>
<th>Location</th>
<th>Subepithelial infiltrates</th>
<th>Ciliary injections</th>
<th>Conjunctival injection</th>
<th>Eyelid skin lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>2 weeks</td>
<td>4</td>
<td>Central</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>Minimal</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>10 days</td>
<td>6</td>
<td>Peripheral</td>
<td>3 weeks Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>4 weeks</td>
<td>5</td>
<td>Central</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>3 weeks</td>
<td>4</td>
<td>Central</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>2 weeks</td>
<td>4</td>
<td>Peripheral</td>
<td>4 weeks Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

**Figure 1** Schematic drawing of active dendritic keratitis in patient no. 3. Note the stromal infiltrates (arrow) and the peripheral location of most of the dendrites.

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tapered to 20 mg per day, while the dosage of the other two medications was not changed. Subsequently the cyclosporin dosage was monitored so that a concentration of 140–200 ng/ml whole blood was achieved. The immunological profile and natural killer activity were not examined routinely in the patients included in the study. It should also be stressed that the patients did not receive preventive systemic acyclovir treatment. None of these patients could recall any previous corneal or eyelid herpetic infection. Three patients out of five had an associated herpetic skin eruption in the lower eyelid on the same side as the affected eye, which appeared several days before the corneal infection. In all five patients the herpetic infection was found to be unilateral, and there were multiple dendrites, most of them located either in the corneal periphery near the limbus (Fig 1) or at the limbus itself. There was no associated ciliary injection, and conjunctival hyperaemia was minimal or absent. Viral cultures taken from the epithelial lesions and the immunofluorescence tests revealed the presence of HSV.

The clinical course of the epithelial disease seemed to be prolonged in all the patients despite treatment with acyclovir ointment five times daily. This treatment had to be continued for three to four weeks until normal looking epithelium was observed. In all patients the course was protracted by small subepithelial nummular infiltrations under some of the epithelial dendrites leading to superficial scarring, without any associated signs of uveitis. The classical picture of disciform keratitis did not develop during a follow-up period of four to six years, and no recurrence was noted in any patient.

Discussion

Viral infections still represent an important cause of complications and failure in the early post-transplantation period as a consequence of heavy initial immunosuppression.\textsuperscript{3,4} Natural killer (NK) cells play an important part in most defence mechanisms against viral infections.\textsuperscript{14} Cauda et al\textsuperscript{15} have presented data which suggest that the impairment of NK cells and T-cell activity is responsible for the increased risk of viral infections in transplant recipients receiving chronic immunosuppression.

The HSV, like the other members of the herpes virus group, has a longstanding close adaptation to its host.\textsuperscript{14} This virus has the capacity to establish latent, persistent infection in neural ganglia and probably also the lacrimal gland.\textsuperscript{14} From these sources it is periodically reactivated, causing viral shedding and transmission to new susceptible hosts and is thus found ubiquitously in all isolated populations.\textsuperscript{11} In addition, Tullo et al\textsuperscript{18} presented data on the isolation of HSV from corneal discs of patients with chronic stromal keratitis.

As much as 80% of the healthy human population is estimated to be infected by HSV-1, but only a small percentage of these manifest herpetic disease.\textsuperscript{19} As this virus has been isolated from the saliva and tears of asymptomatic individuals,\textsuperscript{20} symbiosis appears to be the most common relationship between humans and HSV-1. Both virus and host immune factors may contribute to the maintenance of herpes virus infections at a subclinical level.

We expected, therefore, that herpetic epithelial corneal disease would be more frequent in immunosuppressed recipients. Patients who have had a kidney transplant in comparison with the normal general population, serving as a control group for our study. According to several large epidemiological studies the incidence of dendritic keratitis is difficult to estimate, as many cases are subclinical infections and others are undiagnosed.\textsuperscript{21} It ranges between 59 and 500 new cases per million per year in Denmark\textsuperscript{20,21} and 1 to 1.6 per million per year in Tunis.\textsuperscript{23}

With regard to the results of our retrospective study, about one out of 100 renal transplant patients developed dendritic keratitis, which seems to be a higher rate of infection than the expected rate in the normal population.\textsuperscript{20,21} However, it is lower than the rate of systemic HSV infection or isolation in allograft patients, which ranges widely from 18%\textsuperscript{20} to 66%.\textsuperscript{9}

The clinical course of herpetic corneal disease found in our patients was similar to herpetic keratitis developing in healthy patients following long-term local steroid treatment. These patients also show multiple dendrites, the majority of them located in the corneal periphery.

In three out of five presented patients the virus probably penetrated into the superficial stroma, causing subepithelial keratitis and nummular keratitis leading to superficial scarring, without any associated signs of uveitis. The classical picture of disciform keratitis did not develop. In addition the antiviral treatment had to be continued for at least three weeks in order to eliminate the active viral infection. The fact that none of the patients developed disciform keratopathy is supported by the evidence provided by Metcalf and Kaufman.\textsuperscript{3} They showed that congenitally athymic nude mice failed to develop stromal lesions following corneal infection with HSV-1, while their euthymic litter mates did develop disciform-like stromal lesions.

Russel et al\textsuperscript{30} extended these findings by showing that nude mice could be made susceptible to stromal lesions following adoptive transfer of T lymphocytes from HSV-1 infected euthymic mice.

The atypical clinical picture of HSV keratitis found in our patients is similar to that reported by Howcroft and Breslin\textsuperscript{13} in renal transplant recipients. First, they also found multiple dendrites in the peripheral cornea, adjacent to the limbus; secondly, the keratitis was associated with minimal circumcorneal injection or none at all; and, thirdly, all their patients had assumed herpes virus infections of the skin. The differences are that we did not find evidence for bilateral disease or signs of uveitis, which were both reported by these authors\textsuperscript{13} in 50% of their patients. Moreover, the clinical course of herpetic disease was more prolonged in our patients and necessitated a longer period of antiviral treatment. The postoperative treatment regimen was also somewhat different, as our patients received a combination of steroids, cyclosporin-A, and azathioprine, while Howcroft and Breslin’s patients received steroids and azathioprine only.\textsuperscript{13} Unfortunately these authors\textsuperscript{13} did
not present data on the rate of HSV corneal infection among their patients.

To conclude, HSV corneal disease is a relatively frequent postoperative complication in renal transplant immunosuppressed patients, though less frequent than the overall rate of systemic viral infections in these patients. Furthermore, our patients showed that the clinical course of this corneal infection is atypical and that it is coupled with minimal conjunctival reaction. Therefore one should be aware of this complication in this specific group of patients, mainly during the early postoperative period, when high doses of immunosuppressive medications are given and the NK cell activity of the patients is suppressed.

Ophthalmic consultation should be provided as soon as any mild ocular symptoms develop, though the patient's eyes may look uninflamed.