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François Mosimann
Pierre-François Cuénoud
Florence Steinhäuslin
Jean-Pierre Wauters

Herpes simplex esophagitis after renal transplantation

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F. Mosimann (✉) · P.-F. Cuénoud
Department of Surgery,
University Hospital (CHUV),
CH-1011 Lausanne, Switzerland

F. Steinhäuslin · J.-P. Wauters
Division of Nephrology,
University Hospital (CHUV),
CH-1011 Lausanne, Switzerland

Abstract This paper describes five renal transplant recipients, out of a series of 221 consecutive patients, who developed herpes simplex esophagitis. This opportunistic infection presented as odyno- and/or dysphagia. It occurred during or shortly after treatment of acute cellular rejection episodes with high doses of steroids and, in four cases, of antilymphocyte globulins. The infection responded to acyclovir in all patients. We conclude from these observations that herpes esophagitis occurs during periods of intensive immunosuppression. Because its endoscopic manifestations are variable, biopsies and cultures are essential to reach the diagnosis. Prevention may be possible by avoiding transplantation from a seropositive donor to a negative recipient and by prophylactic oral acyclovir.

Key words Esophagitis, renal transplantation · Herpes simplex esophagitis, renal transplantation Renal transplantation, esophagitis, herpes simplex

Introduction

Esophageal complaints are not usually listed as complications of organ transplantation. However, a review of our renal transplantation activities since the introduction of cyclosporin A as the cornerstone of our immunosuppressive protocol in August 1983 showed evidence of five patients who complained of odyno- and/or dysphagia. The diagnosis of herpes simplex esophagitis was reached in all of them. The aim of this paper is to report their histories, define the risk factors, and propose a prophylactic strategy to prevent this opportunistic infection.

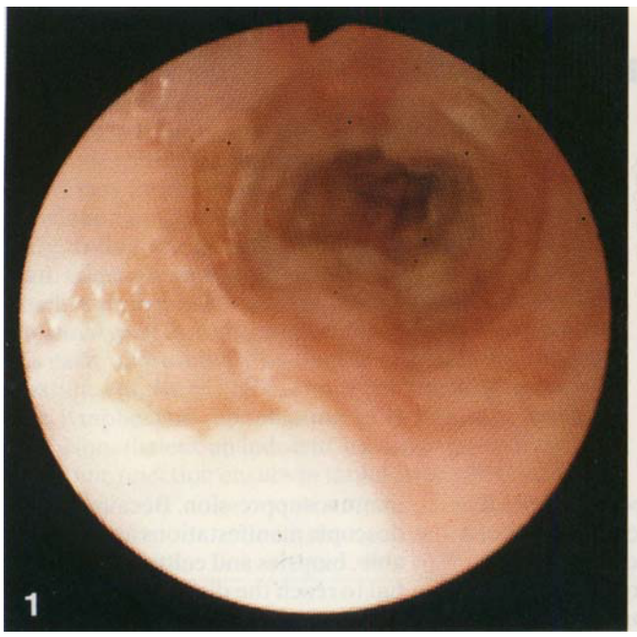
Patients and methods

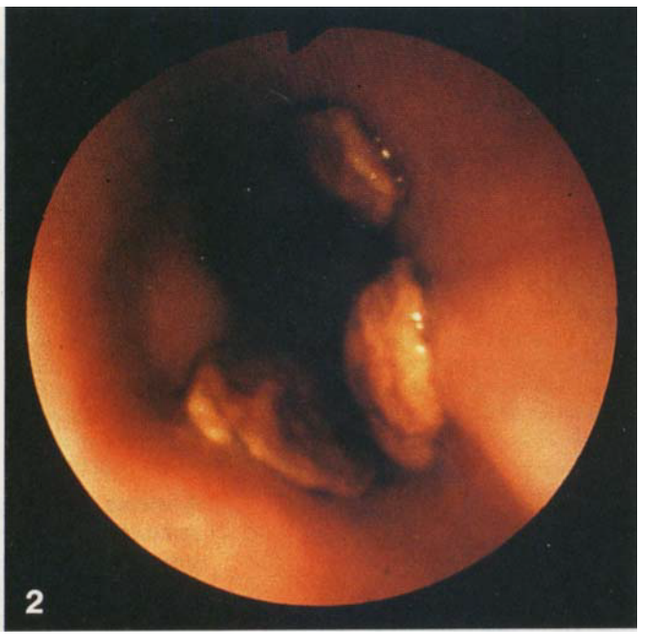
A total of 221 renal transplantations were performed at our center between August 1983 and December 1991. The records of these patients were examined retrospectively for symptoms and signs suggestive of esophageal disease. Only those with proof of herpetic esophagitis were included in the study. The criteria for diagnosis were: (a) macroscopic lesions seen at endoscopy; (b) histological evidence on brushing or biopsy material, such as viral inclusion bodies, and/or (c) positive viral cultures from biopsies or brushings. Immunohistochemistry, although also recommended to confirm the diagnosis, was not performed in this series.

Results

The diagnosis of herpetic esophagitis was made in five patients, all female. This represents 2.2% of the renal transplantations performed during the study period. The five women, aged 32–68 years (average 53 years), received cadaveric grafts from donors aged 19–38 years (average 28 years) with complete ABO and one to three (average two) HLA matches. Three were grafted for reflux nephropathy and two for polycystic disease. All were on chronic hemodialysis at the time of transplantation and had uneventful operations. Their immunosuppressive regimen consisted of low-dose cyclosporin and prednisone, plus azathioprine in one case.

The first common denominator in the posteropative course of these patients was that they all developed acute cellular rejection. This happened early in four, i.e., 4–8





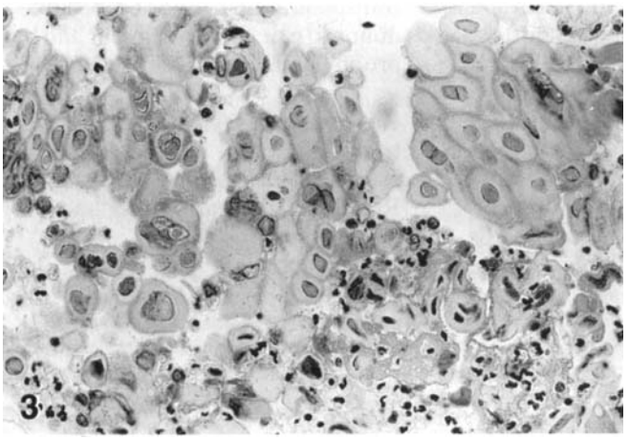


Fig. 1 Herpes esophagitis: shallow ulcers surrounded by vesicles

Fig. 2 Herpes esophagitis: pseudomembranes cover the ulcers

Fig. 3 Multiple herpetic inclusion bodies in esophageal epithelial cells at the margin of an ulcer. (H & E, × 170; Courtesy of Dr. C. Fontolliet)

days post-transplantation, and late in one, i.e., 6 months postoperatively.

Treatment of rejection consisted of high doses of methylprednisolone in all patients: they received 3–9 0.5 g i.v. boluses (average 2.7 g) over a period of a week. In addition, injections of polyclonal antilymphocyte globulin for 8 and 10 days were needed in two cases (Lymphoglobulin Mérieux, 25 mg/day, or ATG Fresenius, 10 mg/day); another two patients received a course of the monoclonal antibody OKT_3 (5 mg/day) for 6 and 8 days.

The second common denominator in our patients was that they all started to complain of odyno- or dysphagia during or shortly after antirejection therapy. These symptoms were investigated by upper GI endoscopy and allowed the diagnosis of herpes esophagitis to be reached in the five patients. All patients also presented orocutaneous lesions, but the esophageal complaints were the inaugural symptoms in two cases.

The endoscopic findings were not uniform: in only one patient could shallow ulcers surrounded by typical vesicles be seen (Fig. 1). In another, the esophagitis was pseudomembraneous, mimicking a cutaneous senile lentigo (Fig. 2). In the other three, discrete or coalescent ulcers were observed, suggesting plain reflux esophagitis.

The diagnosis was confirmed in all patients by histology (Fig. 3) and by culture in four. The only negative culture was recorded in the patient with the very suggestive vesicles shown in Fig. 1; similar lesions developed on the lips and in the mouth 2 days later.

All patients responded well to i.v. acylovir and a marked reduction in the immunosuppressive therapy. All left the hospital with a functioning graft (creatinine 116–224 mmol/l; average 169 mmol/l), although two transplants were eventually lost, due to chronic rejection after 7 and 9 months.

Discussion

Herpes simplex esophagitis was recognized 50 years ago [13, 25]. It occurs very rarely in healthy, immunocompetent sujects [8–10, 23, 28]. For instance, only 1 of 23 patients recently reported from the Mayo Clinic was not immunodeficient. The others had malignancies, AIDS, or were taking immunosuppressive drugs [18]. Only two were kidney transplant patients, and the present modest series of five may well be the largest ever reported in that population. Since our center is small, performing 25–35 renal allografts each year, this probably means that this diagnosis is often missed, especially in otherwise very ill patients. A delay in treatment may, however, have devastating consequences as the infection can progress to hemorrhage, sometimes fatal [12, 21, 23, 26], or to spontaneous esophageal perforation [7]. In addition, infection, especially viral, is known to decrease renal allograft and recipient survivals, both at 1 and 3 years [4]. This deleterious effect is evident even in a small series like ours, as two of the five transplants were eventually lost, due to chronic rejection, whereas the overall actuarial graft survival for the study period was 90%. Infection with cytomegalovirus early after engraftment is, indeed, regarded by many as a risk factor for chronic rejection, and it has recently been suggested that this may parallel the possible correlation between atherosclerosis and herpes infection [30].

All of our patients were women; as this has not been described in other series, we feel that this is a chance event and that female sex is not to be regarded as a risk factor.

The potential hazards related to herpes simplex esophagitis should enhance an aggressive diagnostic and therapeutic policy whenever a transplant recipient presents with esophageal symptoms, even if these are minimal.

The index of suspicion must be high in periods of increased immunosuppression, as during treatment of rejection with large doses of steroids; it must be at its highest when poly- or monoclonal antibody antilymphocyte preparations are added, as in four of our five patients [22]. In this setting, the period of greatest risk for opportunistic infections is the 1st month; it may, however, last for as long as 3 months [4] and the disease may be heralded, as in two of our patients, by odyno- or dysphagia. These symptoms call for immediate endoscopy in order to secure an accurate diagnosis and initiate a specific treatment. Typical vesicular lesions surrounding ulcers, as seen once in the present series, are a rare observation. They probably represent an early stage of the infection, soon followed by necrosis, exudation, and sloughing [19, 20]. Although it has not been supported by serial endoscopic studies in individual patients, this progression of the lesions could explain the variability of the findings [6], as peptic-like inflammation [16], small discrete ulcers [15], volcano ulcers [1, 7], multiple coalescent ulcers, and pseudomembraneous esophagitis have all been described [18]. This variability is compounded by the fact that other opportunistic microorganisms, mostly cytomegalovirus and *Candida* [24], can also cause esophagitis in immunocompromised patients, either alone or in combination [3, 5]. Biopsies should, therefore, be taken in such cases for histological examination, viral cultures and, ideally, immunohistochemistry. In the present series, the only patient with negative cultures was the case with the highly suggestive vesicular lesions (Fig. 1). Like Kadakia [14], we suspect that this negativity was due to the early stage of the infection.

Treatment of herpes simplex esophagitis is intravenous, and later oral, acyclovir, a virostatic agent that interferes with DNA synthesis. Moreover, immunosuppressive medications must be sharply decreased or even discontinued until the life-treatening situation has been mastered. Prevention of herpetic esophagitis is a more debatable topic. Theoretically, a policy of systematic herpes simplex screening could eliminate the risk of primary infection in a seronegative recipient by an allograft from a positive donor [11, 17]. In view of the present shortage of transplantable organs, such a restrictive strategy does not, however, appear to be a realistic option. Instead, should herpes simplex screening become universal practice, acyclovir can be administered prophylactically in case of a positive-negative donor-recipient pair, possibly with the concomitant injection of nonspecific human immunoglobulins [29]. Like many other teams, we have, indeed, been practicing such a policy for cytomegalovirus-negative recipients transplanted with a kidney from a positive donor. This may be why we have not encountered a single case of esophagitis caused by this virus during the period under study. For the herpes simplex-positive recipient, oral acyclovir after transplantation may also be ordered, whatever the serologic status of the donor, because it is capable of suppressing reactivation of the virus, as well as that of varicella zoster and cytomegalovirus [2, 27]. Such a general use of this drug can be questioned in view of the small prevalence of severe herpes simplex infections in solid organ recipients. Further reducing this prevalence and the severity of symptomatic illnesses may, however, justify the additional expense.

In conclusion, herpes simplex esophagitis in renal transplant recipients is a potentially life-threatening, opportunistic infection. It occurs in times of intensive immunosuppressive therapy, as during or after treatment of rejection episodes. Odyno- and/or dysphagia call for endoscopy with biopsies for histological examination, immunohistochemistry, and viral cultures. Treatment by acyclovir and concomitantly reduced immunosuprression is effective. Prevention is possible by oral acyclovir after transplantation.

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