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INTRODUCTION

The International course on transplantation and clinical immunology (CITIC) takes places in LYON every years in May or June. In this volume will be found the documents presented during the 9 th session of the CITIC.

The CITIC was born in 1967, during the expanding phase of clinical Transplantation vhen the need for information of many physicians wanting to develop transplantation centers was obvious.

Over the following years our objectives became larger : the initial topics which refered to organ transplantation - kidney, heart, pancréas... - became more and more oriented in the general field of clinical immunology, without neglecting the annual up-to-date reports on clinical organ transplantation, its organisation and strategy. Now two or three important subjects in the fields of transplantation Immunology - Immunovirology - Immunopathology - Immunohematology, etc... are studied each years. These lectures are followed by workshops during which the pratical aspects of laboratory technics are carefully studied.

However, these slow changes and new orientations, have not altered the aims and goals that we had initially choosen, i.e to present every year high level symposia with up-to-date reports on subjects of direct or indirect interest for transplantation.

The communications are gathered in day or half a day sessions and are presented by the most advanced international specialists in the field. These high level sessions have given its interest and fame to the CITIC. We believe that the qualities of the presented lectures and the following discussions represents both an important scientific advance and an emulation for the participants.

Until now the proceedings of these CITIC, attended by a large international audience were published in France -partly in french, partly in english. We hope that this new presentation and the vast diffusion which will take place through Excerpta medica will permit an increased number of physicians and scientist to know more about the CITIC.

J. TRAEGER.

Herpesviruses and transplantation

CLINICAL ASPECTS OF INFECTIONS DUE TO HERPESVIRUSES IN RENAL TRANSPLANTS RECIPIENTS*

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Herpesviruses include : 1) herpes simplex viruses, type 1 and type 2 (HSV_1 and HSV_2); 2) B virus, responsible for encephalitis in primates, exceedingly rare in man; 3) herpes zoster virus (HZV) which may also cause varicella; 4) Epstein-Barr virus (EBV), responsible for infectious mononucleosis and presumably Burkitt lymphoma; 5) cytomegalovirus (CMV).

HSV_1 and HSV_2 may both produce encephalitis but HSV_1 is responsible for facial and corneal lesions, and HSV_2 for skin lesions of the anogenital region. Moreover, HSV_2 may play an important part in the pathogenesis of carcinoma of uterine cervix (1). CMV infection may produce various clinical pictures, mainly pneumonitis, hepatitis and infectious mononucleosis-like syndrome.

In renal transplant recipients, the following pictures are usually observed : 1) cutaneous and corneal lesions due to HSV_1, 2) herpes zoster or less often varicella, 3) CMV hepatitis and CMV pneumonitis. Moreover autopsy reveals typical CMV inclusions within the brain, pancreas, transplant, etc. in patients who never experienced clinical manifestations of these localizations. Finally, in asymptomatic transplant recipients, CMV is often cultivated from urine (2), and seroconversion to HSV or CMV may be observed (3).

The high incidence of infections due to herpesviruses in kidney transplant recipients, with three serious localizations (cornea for HSV, lung and liver for CMV), led us to analyze them within a group of patients observed in a single institution.

PATIENTS AND METHODS

1. Patients

The group of recipients under study consisted of 220 patients who received 262 renal grafts between March 1, 1965 and December 31, 1976. In 28 cases, the graft was obtained from related living donors while brain-death donors supplied 234 kidneys. Immunosuppressive therapy consisted of azathioprine, prednisolone and local irradiations. From May 1969 to December 1975, it also included antilymphocyte globulins, administered during 0.5 to 3.0 months. These globulins were obtained from horses immunized against lymphoblasts (Behring Werke, Germany) or thoracic duct lymphocytes (Institut Mérieux, France). As the incidence and severity of viral infections did not differ significantly in patients treated with globulins and in untreated patients, no distinction was made between the two groups.

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2. Diagnosis of viral infections

The clinical manifestations of herpes simplex, varicella and herpes zoster were obvious enough but some of the skin lesions due to HSV may have been overlooked. The diagnosis of CMV pneumonitis was established by virus isolation from lung tissue or bronchial secretions and/or by the demonstration of characteristic cells in lung tissue obtained by biopsy or at autopsy in patients with diffuse pneumonitis. Moreover, from January 1975, monthly sera of the patients were routinely screened for CMV antibodies.

For CMV hepatitis, the diagnosis was suggested when seroconversion preceded or accompanied biological and/or clinical signs of hepatitis. In the absence of liver biopsies, the diagnosis of CMV hepatitis was thus established on weaker grounds than for the other localizations of herpesviruses infections. Despite these drawbacks, it was found necessary to scrutinize the hepatitis occurring in renal transplant recipients, owing to its high incidence and because CMV is apparently as prevalent as hepatitis B virus (HBV) in this respect.

RESULTS

1. HSV infections

Thirty-six patients had 48 HSV infection episodes : 8-22 % of all transplanted patients, according to the year considered. HSV infections, which were not more prevalent in eldest patients, occurred mainly during the first 6 postoperative months (54 % of all HSV infections), 75 % of all episodes taking place during the 1st year. The sites of the lesions were lips (36 episodes), nose (1 episode), eyelids (1 episode) and cornea (9 episodes). Keratitis, a very distressing condition, showed a marked tendency for recurrence, 9 episodes being observed in 4 patients. Thirty-three of the 48 HSV episodes supervened 2-74 days after a transplant crisis and followed thus increased corticotherapy. In 3 patients, HSV infection preceded rejection crisis by 2-42 days. In 12 cases, it was not related to rejection.

2. HZV infections

Twenty-eight HZV infectious episodes were observed in 27 patients, with an incidence of 3-20 %, according to the year under consideration. HZV infections occurred more frequently in patients over 50 years : this age group represented 23 % of all HZV infections while it constituted only 8 % of all graft recipients. In contrast with HSV infections, HZV infections occurred evenly in all postoperative periods : 25 % in 1st semester, 11 % in 2nd semester, 32 % in 2nd year, 11 % in 3rd and 4th year , 11 % over 4th year. In comparison, amoung the 350 patients admitted into our current hemodialysis program, 5 HZV infection episodes were observed from 1965 to 1976.

The sites of the HZV lesions were : thoracic (17 cases), sacro-lumbar (7 cases), cervical (2 cases), trigeminal (1 case), varicella (1 case). In 4 cases, the lesions were necrotic and/or hemorrhagic and 1 case of lumbar eruption was accompanied by severe intestinal ileus. In 1 patient, HZV lesions recurred at the same site at 1 year interval.

3. CMV infections

1) Seroconversions in patients on dialysis

Before analyzing CMV infections in kidney graft recipients, it is necessary to present as control the incidence of CMV infections in our dialysis unit. Among 40 patients observed from June 1975 to December 1976 (25 who were never grafted and 15 who underwent 1 or 2 transplan-

tations), 14 CMV seroconversions were observed, 6 occurring in patients without previous transplantation. In 10 patients, seroconversion remained asymptomatic. It was followed, after 1-5 months, by biological and/or clinical signs of hepatitis in 4 patients. CMV pneumonitis was never observed in dialyzed patients.

2) Seroconversion in kidney graft recipients

Among 81 recipients, 51 seroconversions were observed, with the following time-course : 19 in 1st year, 15 in 2nd, 5 in 3rd, 5 in 4th, 3 in 5th and 1 over the 5th postoperative year. In 22 patients, seroconversion was asymptomatic. In 4 cases, it was followed by transplant crisis, and in 4 other patients, by persistent proteinuria. In 21 kidney recipients, seroconversion preceded biological and/or clinical signs of hepatitis (Fig.1).

Comparison between dialyzed and transplanted patients demonstrates that CMV seroconversion took place with greater frequency ($P < 0.001$) in graft recipients than in dialyzed patients who never received a transplant, but the difference was not significant ($0.70 < P < 0.80$) if the comparison was made with the 15 dialyzed patients who had been grafted previously.

3) CMV pneumonitis

Among our 220 kidney recipients, 10 cases of CMV pneumonitis were observed (4). Nine patients died despite respiratory assistance, after intervals from 3 to 31 days. The illness supervened during the 6 postoperative months in 7 patients, and after 13, 18 and 38 months, in the 3 other cases. In 3 patients, CMV pneumonitis occurred without relation to transplant crisis, but, in the other 7 cases, it followed such an episode by 17-54 days.

In 5 cases, another lung infection was associated : Pneumocystis carinii in 2, fungi in 2, bacteria in 1 patient. In 3 cases, autopsy revealed typical nuclear inclusions in brain, liver and/or graft. CMV was cultivated from lung tissue or bronchial secretions.

In 7 patients, CMV pneumonitis was accompanied by a decrease in graft function, necessitating the return to dialysis for 2 patients, including the only one who recovered from pneumonia. In 1 case, reduction of kidney function was due to recurrence of primary glomerulopathy in the graft but, in the 6 other recipients, histologic examination of the transplant showed the usual features of rejection.

4) CMV hepatitis

Among the 81 kidney recipients under survey, 31 showed biological and/or clinical signs of hepatitis, which were transient in most cases. Among these 31 patients, 7 had been or were still HB_sAg carriers, 14 had demonstrated CMV seroconversion, 5 had been or were still HB_sAg carriers and had also demonstrated CMV seroconversion. HB_sAg and CMV seroconversion were never demonstrated in the remaining 5 recipients (Fig.2). Thus, 17-23 % of the 81 kidney recipients may have developed CMV hepatitis; in 8-15 %, HBV may have been responsible for hepatitis, and other viruses, such as HAV or EBV, may have been the causal agents in 6 % of patients.

Within the whole group or kidney recipients, 12 cases of chronic hepatitis were observed. Table 1 shows that in 3-6 of these 12 patients, CMV may have been responsible for this disease.

TABLE 1 Hepatitis persisting over 12 months in 220 patients submitted to kidney transplantation between 1965 and 1976

HB_SAg	CMV Seroconversion	Numbers
Positive	Negative	4
Negative	Positive	3
Positive	Positive	3
Negative	Negative	2
	Total	12

CONCLUSIONS

Infections due to herpesviruses play undoubtedly a major part in morbidity and mortality of kidney graft recipients. The most important of them is CMV, which led to fatal respiratory failure in 4.5 % of our 220 patients. CMV may also be responsible for hepatitis in about 20 % of kidney recipients. In a few cases, CMV hepatitis may run a chronic course, as may also be observed for hepatitis B virus.

In many cases, increased corticotherapy for control of graft rejection seems to be responsible for most infections due to herpesviruses. Table 2 however shows that about 10 % of such infections may have been responsible for decreased graft function. Here again, CMV seems to play the major role, its occurrence leading to persistent proteinuria (due to immunocomplexes ?) or to decrease in glomerular filtration rate (due to cross-reacting antigens ?).

TABLE 2 Herpesviruses infections which may have affected renal function in 262 kidney grafts

Viruses	N° of Cases with Decreased Graft Function	Total N° of Infectious Episodes
HSV	3 (6.3 %)	48
HZV	2 (7.1 %)	28
CMV	8 (15.7 %)	51
Total	13 (10.2 %)	127

Comparison between CMV and hepatitis B virus in kidney recipients shows an important difference between the two viruses. Recipients who are or have been HB_SAg carriers have better graft survival than HB_SAg negative recipients (5) while CMV may be responsible for transient or permanent damage to the graft. This latter observation is at variance with the experience of Simmons et al. (2) who reported that CMV pneumonitis was usually accompanied by lack of graft rejection while CMV seroconversion without pneumonitis was usually marked by acute graft rejection which responded favorably to increased corticotherapy. No satisfactory explanation can be offered for this discrepancy, but it may be due to differences in methodology, perhaps in definitions of seroconversion.

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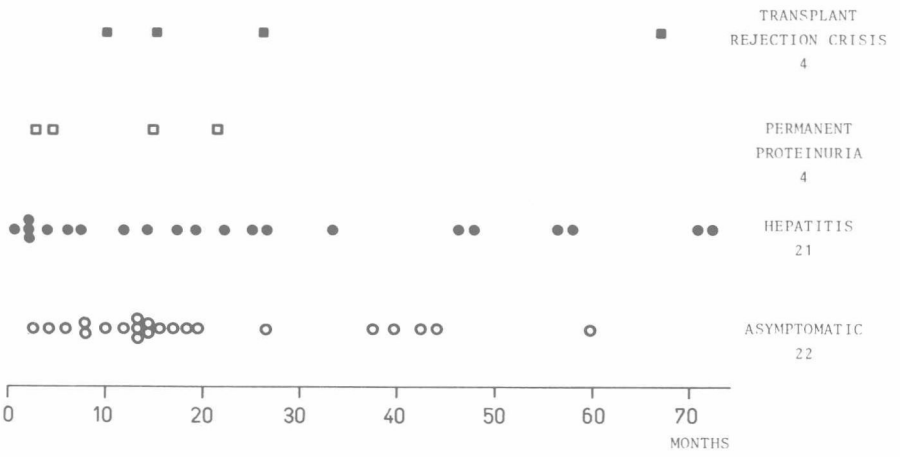

FIG. 1 CMV seroconversion in 81 kidney graft recipients.

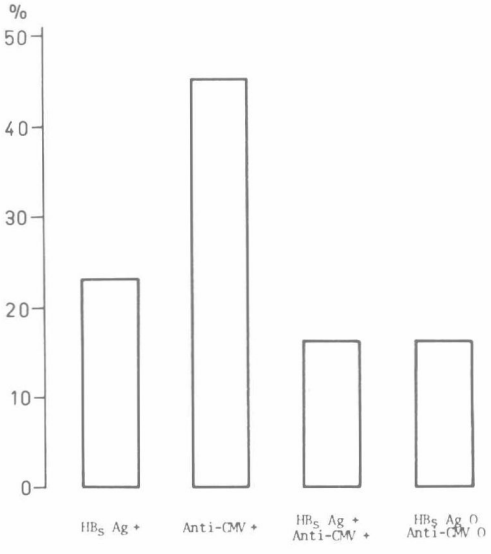

FIG. 2 31 cases of hepatitis in 81 kidney graft recipients.

ADVENTURES IN LATENCY AND REACTIVATION OF CYTOMEGALOVIRUS: FACTS AND FANTASIES*

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A particularly puzzling and challenging biological problem in medicine concerns the behavior of cytomegalovirus (CMV) infection. A DNA virus in the herpes virus family, CMV infects humans and causes significant birth defects and subtle dysfunctions in behavioral, visual and auditory systems of developing children and juveniles (1-3). Additional dysfunctions, especially in the cardiovascular, pulmonary and hepatic systems, are possible sequelae of earlier or ongoing CMV insult. Clinical disorders following transplantation or open heart surgery are often associated with CMV infection. Possibly this infection is transmitted in the multiple transfusions of fresh blood (containing living leukocytes) and by the immunosuppressive drugs that these patients so frequently receive. Further, CMV persists in the host it infects, despite the host's vigorous immune response. Hence, man and CMV is a model system *par excellance* for studying virus latency, persistence and reactivation.

The clinical states listed in Table 1 are associated with a history of prior CMV exposure, suspected viral latency and reactivation. This list suggests that a graft vs. host or host vs. graft reaction might well be a common thread in this infection's effects.

TABLE 1 CMV infection associated with:

1. Pregnancy
2. Organ transplantation
3. Multiple blood transfusions
4. Immunosuppression
5. Malignant lymphomas

Using techniques depicted in Figure 1, my colleagues and I were able to show the activation of murine CMV (MCMV) from spleen lymphocytes of latently infected mice (Table 2) (4, 5). Further, we noted that activation was dependent on at least three factors: (1) appropriate antigenic stimulation, (2) activating or responding cells carrying the genetic capacity to express virus information, and (3) the need for a feeder layer of cells that were susceptible to infection and permitted the virus to replicate, once activated. Using classical immunologic depletion and reconstitution assays, we were able to show that the bone marrow-derived (B) enriched lymphocyte population harbored MCMV, whereas we were unable in multiple experiments to recover virus from thymus-derived (T) lymphocytes obtained from spleen or thymus glands (4). In all these experiments virus was recovered after allogeneic stimulation and co-cultivation, but in no study was virus activated by co-cultivation on permissive syngeneic cells (Table 2). Additional experiments supporting the concept that MCMV is harbored in the B enriched population of cells employed T-less nude mice or the application of a B cell mitogen, lipopolysaccharide (LPS) (4). As seen in Table 3, MCMV was easily recovered from susceptible syngeneic or allogeneic fibroblasts from spleens of T-less nude mice depleted of adherent cells. Further, virus could be recovered from frozen and thawed or sonicated spleen cell lymphoid preparations from these mice, indicating that MCMV was present in an infectious form. When lymphoid

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