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## CMV ALLOGRAFT PANCREATITIS: Diagnosis, Treatment, and Histological Features

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### Abstract [TOP](#)

Background. Cytomegalovirus (CMV) infection is a common problem in solid organ transplant recipients. CMV infection of pancreas allografts is not, however, well described.

Methods. We report the clinical presentation, histologic findings, treatment, and outcome in four patients with CMV allograft pancreatitis. These patients presented 18 weeks to 44 months after transplantation with elevated serum amylase and lipase and were suspected to have acute rejection. Percutaneous pancreas allograft biopsy specimens showed evidence of tissue invasive CMV infection. One patient had simultaneous CMV infection and acute rejection.

Results. Prolonged treatment with ganciclovir resulted in clinical and histologic resolution of the CMV disease. Rejection

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was successfully treated. Primary CMV infection in seronegative recipients seemed to be a risk factor. Three patients maintain normal allograft function; one patient lost function due to chronic rejection. The histology of tissue-invasive CMV pancreas allograft infection and its differentiation from acute rejection is described.

**Conclusion.** Prompt diagnosis and prolonged therapy with antiviral agents can result in maintenance of allograft function.

Cytomegalovirus (CMV) infection is a major complication after organ transplantation. It can produce a variety of clinical syndromes and may result in direct allograft damage as well as predispose to subsequent rejection. CMV infections are reported to occur in up to 60% of kidney transplants (1). Many infections are, however, asymptomatic. The frequency of direct allograft infection and its significance is unclear. In kidney transplant recipients CMV viremia is common, but histologic evidence of kidney infection is much less common and its clinical significance remains controversial (2-4). CMV infection of pancreas allografts has rarely been reported (5,6). Most cases have been based on clinical findings compatible with systemic infection in conjunction with biochemical evidence of graft pancreatitis. The histology of CMV allograft pancreatitis is not well defined, and the clinical presentation and diagnostic strategies in these cases are unclear. The outcome of suspected cases of CMV allograft pancreatitis has been reported to be poor (5,6). Distinguishing CMV allograft pancreatitis from acute rejection on clinical grounds is difficult. This distinction is however important because treatment strategies for these entities are very different. In this report we described the clinical and histologic findings in four cases of biopsy-proven CMV allograft pancreatitis and the treatment and outcome of these cases.

We analyzed the clinical parameters and pathological findings in pancreas transplant patients with CMV inclusions and immunohistochemical evidence of CMV infection on pancreas allograft biopsy. Cases and data were obtained from 236 technically successful pancreas transplantations done at the University of Maryland Medical Center from 1993 until 1997 and consisted of 129 simultaneous pancreas kidney (SPK) transplants, 74 pancreas after kidney transplants, and 33 pancreas transplants alone (PTA). This represents all pancreas transplants done after the introduction of routine percutaneous pancreas allograft biopsy into our clinical practice and allows at least 1 year of clinical follow-up for all patients in the cohort.

Four patients with histological evidence of CMV pancreas allograft infection were documented. The biopsy specimens were obtained using an 18-gauge automated biopsy needle under ultrasound guidance. Biopsy specimens were obtained to evaluate elevations in serum amylase or lipase or unexplained fever. Histological evaluation of these biopsy specimens for rejection followed previously published guidelines (7,8). Tissue-invasive CMV infection was identified by the presence of cytoplasmic or intranuclear inclusions and cytomegaly. Hematoxylin and eosin (H&E) and Masson's trichrome stains were examined in 4- $\mu$ m sections. Suspected CMV allograft pancreatitis was confirmed by specific immunoperoxidase stains for CMV (Dako, Carpinteria, CA). Clinical information on these cases was obtained by review of medical records. CMV infections were additionally evaluated by assay of circulating CMV pp65 antigen in blood and by cytopathic changes in tissue culture of blood. Serologic evaluation of anti-CMV IgG and IgM levels was obtained before transplantation in all cases.

The demographic features of these patients are shown in [Table 1](#). Three patients were SPK cases and one was PTA. Three of four recipients were CMV serologically negative at the time of transplantation and all donors were CMV IgG positive. After transplantation, all patients had initial antibody induction with 14 days of antithymocyte globulin (ATG) followed by maintenance immunosuppression with cyclosporine or tacrolimus and steroids. One patient received mycophenolate mofetil. Patients received CMV infection prophylaxis with intravenous ganciclovir at 5 mg/kg twice a day for 2 weeks followed by oral acyclovir at 800 mg three times a day for a total of 14 weeks. All four patients had at least one episode of acute cellular rejection of the pancreas allograft treated with OKT3 or ATG before the diagnosis of CMV allograft pancreatitis. The clinical findings at the time of diagnosis of CMV pancreatitis are summarized in [Table 2](#).

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Table 1. Patient demographics and clinical characteristics

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Table 2. Rejection history, clinical characteristics, and CMV treatment<sup>a</sup> Abbreviations used in table ACV, acyclovir; GCV, ganciclovir.

Patient 1 presented 5 weeks after SPK with elevations of serum amylase and lipase. A pancreas allograft biopsy specimen documented moderate acute rejection, which was treated with 10 days of OKT3. Nine weeks later the patient developed elevated serum amylase and lipase and pancreas allograft tenderness. The initial clinical impression was acute rejection. Percutaneous allograft biopsy showed CMV inclusions in acinar tissue, and immunohistochemical stains for CMV were positive. Intravenous ganciclovir was begun. Two days later the CMV circulating blood antigen was found to be positive. Three days later a pancreatic allograft cyst was drained. Subsequent endoscopy showed esophagitis, gastritis, and duodenitis, biopsies of which grew CMV 2 weeks later. The patient received 7 weeks of intravenous ganciclovir. Four months later rejection of the pancreas was diagnosed by biopsy. No histologic evidence of CMV was seen, and CMV cultures and antigen assays were negative. The patient was again treated with OKT3. Twenty-six months later he resumed insulin with graft failure attributed to chronic rejection.

Patient 2 developed isolated acute pancreas allograft rejection 8 weeks after SPK. This was diagnosed by biopsy and treated with 14 days of OKT3. Cyclosporine was changed to tacrolimus. The biopsy specimen showed no evidence of CMV infection. Five months after transplantation the patient developed fever. The CMV pp65 blood antigen was positive. Because of elevations in serum amylase and lipase, a pancreas biopsy was done. There was no evidence of CMV pancreatitis. The patient was treated with 5 weeks of intravenous ganciclovir followed by 12 weeks of oral acyclovir. Ten months after transplantation, elevations in amylase and lipase developed. A pancreas allograft biopsy specimen showed CMV inclusions. The patient received 4 weeks of intravenous ganciclovir followed by 12 weeks of oral ganciclovir with resolution of the biochemical abnormalities. Twenty-seven months after transplantation the patient complained of nausea. Serum amylase and lipase were elevated. A biopsy specimen of the pancreas allograft showed mild acute cellular rejection and again had CMV inclusions and positive CMV immunoperoxidase stains. The patient received 4 weeks of intravenous ganciclovir followed by continued oral ganciclovir with intravenous high-dose corticosteroids for rejection. The patient's biochemical abnormalities resolved, and pancreas allograft function remains normal 37 months after transplantation.

Patient 3 developed acute pancreas allograft rejection manifested by elevated serum amylase and lipase 5 weeks after PTA. This was diagnosed by biopsy and treated with 14 days of OKT3. No histologic evidence of CMV infection was found. Fifteen weeks after transplantation, rejection again developed in a similar fashion and was treated with ATG for 6 days. Seven months after transplantation the patient developed asymptomatic elevation of amylase and lipase. A biopsy specimen of the pancreas showed both moderate acute cellular rejection and CMV inclusions confirmed by CMV immunohistochemical stains. The patient was treated with intravenous ganciclovir for 4 weeks and ATG followed by oral ganciclovir for 14 weeks. Follow-up biopsy 3 weeks later showed minimal, resolving, acute rejection and no evidence of CMV. The patient continues to maintain good graft function 36 months after transplantation.

The fourth patient developed acute pancreas allograft rejection 4 weeks after SPK manifested by isolated elevation in amylase and lipase. OKT3 was given for 10 days. Six months after transplantation fever developed. Blood cultures were positive for CMV, and serum amylase and lipase were elevated. A pancreas biopsy specimen did not show rejection or evidence of CMV. Intravenous ganciclovir was administered, and the fever and biochemical abnormalities resolved. Eight months after transplantation the patient developed native pancreatitis related to common bile duct stones. These were removed endoscopically. Forty-one months after transplantation the patient developed nausea and vomiting with elevations of amylase and lipase. A pancreas allograft biopsy specimen showed no acute rejection and no evidence of CMV infection. The clinical and biochemical findings were attributed to native pancreatitis and resolved with conservative therapy. Three months later the patient developed low-grade fever and diarrhea and elevations of amylase and lipase. A biopsy specimen of the pancreas allograft showed CMV inclusions confirmed by immunohistochemistry. This resolved with 4 weeks of intravenous ganciclovir followed by oral therapy. The patient maintains good allograft function 47 months after transplantation.

Histologic evaluation of the allograft pancreas biopsy specimens in these patients demonstrated multifocal, predominantly acinar mononuclear inflammation in association with cells displaying the characteristic cytopathic changes ([Fig. 1](#)). These

consisted of marked cellular enlargement, smudging of the chromatin, intranuclear acidophilic inclusions with surrounding halos, and granular basophilic cytoplasmic inclusions. Cells with viral cytopathic changes stained strongly positive with immunoperoxidase stain for CMV.

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Figure 1. CMV pancreatitis. Focus of acinar inflammation and destruction. There are scattered cells with cytomegaly and smudged chromatin (solid arrows) consistent with cytomegalovirus cytopathic changes. (H&E, original magnification  $\times 400$ ). Insert: Immunoperoxidase stain for CMV is strongly positive in one enlarged nucleus (clear arrow, original magnification  $\times 250$ ).

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Histologically identified CMV allograft pancreatitis was found in 2% of pancreas transplant recipients at our center. Previous reports of this entity are very limited and the clinical outcome has been poor. Margreiter et al. (5) reported four cases of clinical CMV pancreatitis. Three of four grafts were lost. Backman et al. (6) noted the development of allograft abscesses in five of eight patients felt to have CMV pancreatitis based on clinical criteria. Graft survival was 50%.

The outcome of tissue-invasive CMV infection in other allografts is controversial. Kashyap et al. (4) described 10 cases with CMV inclusions in allograft kidneys and felt that with antiviral therapy CMV infection did not contribute to allograft loss. Primary CMV infection as occurs when CMV donor-positive organs are transplanted into CMV-seronegative recipients is a known risk factor for severe CMV infection (1), prompting the development of the variety of prophylactic antiviral strategies. In our group of pancreas transplant patients, primary CMV infection seemed to be a risk factor for the development of tissue-invasive CMV pancreatitis because three of four cases occurred as primary infection. This represents an incidence of 5% in our subpopulation of 59 pancreas transplant recipients at risk for primary CMV infection. This occurred despite the use of acyclovir antiviral CMV prophylaxis. Oral ganciclovir has since replaced acyclovir at our center. In addition, all four patients had rejection treated with antilymphocyte antibodies before the development of CMV pancreatitis, which has been shown to predispose to CMV infection in other organ transplant patients. These patients did have antiviral CMV prophylaxis reinstated during treatment of acute rejection.

The clinical presentation of CMV pancreatitis can vary widely. It may present as part of a systemic syndrome with fever and evidence of invasive disease at other sites such as the gastrointestinal tract. One patient had cystic changes in the pancreas similar to observations by Backman et al. (6). Two of four patients had circulating virus in their blood and symptoms suggestive of systemic illness. It can also present as an apparently isolated event without evidence of systemic illness and manifest only elevation of serum amylase and lipase. In this situation it is impossible to differentiate CMV pancreatitis from acute rejection on purely clinical grounds. In most cases this distinction can be made by percutaneous allograft biopsy. Patients 2 and 4 both had an episode of CMV infection associated with elevated serum amylase and lipase values but with pancreas biopsy specimens not showing CMV inclusions. This suggests that a biopsy specimen free of CMV inclusions does not rule out CMV pancreatitis and that systemic cultures and serology remain important. Additional pancreas transplant patients had CMV infection associated with fever, leukopenia, or diarrhea but without evidence of pancreas dysfunction and were not biopsied. The overall incidence of CMV infections is substantially greater than the 2% who had documented tissue-invasive pancreatitis.

A histologic diagnosis of CMV pancreatitis is made on the basis of epithelial, endothelial, or stromal cells with the typical CMV-related cytopathic changes. This diagnosis should be confirmed with immunoperoxidase stains for CMV. The diagnosis of CMV pancreatitis is further complicated by our findings that histologically identifiable CMV allograft pancreatitis can coexist with acute rejection. The diagnosis of concurrent acute allograft rejection is made in the presence of endotheliitis in veins and/or arteries and mixed inflammatory infiltrates often including eosinophils in areas away from the cells with viral cytopathic changes. Pure acinar inflammation in acute allograft rejection and in CMV pancreatitis are indistinguishable from each other if the virally infected cells are not demonstrable due to sampling. The latter problem is minimized by the systematic evaluation of multiple consecutive sections (ribbon sections) in the H&E stained slides. The best utilization of the tissue core is done when from the beginning multiple slides are cut (with several sections each) and every other section is stained with H&E. The unstained sections are then available for ancillary studies and used as necessary. In patients with pancreas biopsy specimens showing nonspecific inflammation but clinical suspicion of CMV infection, the performance of immunoperoxidase stains for CMV even in the absence of typical viral cytopathic changes can in rare occasions yield a positive result. An aggressive attempt to establish this diagnosis including allograft biopsy,

viral cultures, and assay for circulating CMV antigen is appropriate because in our experience an early and accurate diagnosis allows simultaneous treatment of both CMV pancreatitis and acute rejection with maintenance of good allograft function. In our patients no graft loss could be attributed to CMV infection. Follow-up biopsy specimens documented histologic resolution of CMV pancreatitis in three patients. We did observe recurrent CMV disease in one patient. As noted by Humar et al. (3) up to one third of kidney transplant recipients who developed CMV infection will have recurrent CMV disease. This suggests that prolonged courses of antiviral therapy and a decrease in immunosuppression, if possible, may be appropriate.

We conclude that with appropriate diagnosis and with current antiviral therapy the negative impact of CMV infection on pancreas allografts can be minimized.

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