

ORIGINAL ARTICLE

Pancreatitis and adenoviral infection in children after blood and marrow transplantation

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Pancreatitis is a well-recognized consequence of blood and marrow transplantation (BMT). In a 4-year period, between January 2001 and December 2004, five children who received a BMT in our institution were diagnosed as having pancreatitis. Four of these five children also had adenoviral infection. We report these four cases and highlight the importance of investigating for pancreatitis patients who have any abdominal symptoms post BMT, and include specific stool culture for viral isolation, if it is not already known.

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Introduction

The reported incidence of adenovirus infections post transplantation varies between 4.9 and 41%.^{1–8} In immunocompetent children, adenovirus is endemic and usually causes a mild self-limiting illness such as an upper respiratory tract infection, gastroenteritis, conjunctivitis or haemorrhagic cystitis. However, in the immunocompromised, adenovirus infections can be more severe. In this group of patients and particularly those after blood and marrow transplantation (BMT), adenovirus infection can be asymptomatic or cause localized disease, such as a respiratory tract infection, infectious gastroenteritis and haemorrhagic cystitis, or become more invasive, causing hepatitis, nephritis, pancreatitis or meningoencephalitis.^{9–15} Such dissemination of adenoviral disease is associated with a significant mortality.^{6–8,16}

Pancreatitis is recognized as a complication of BMT. This can be related to many factors involved in the

transplantation procedure, including drugs administered known to cause pancreatitis, the conditioning therapy, graft-versus-host disease (GVHD)¹⁷ and infections.^{18,19} It is reported that adenovirus can cause pancreatitis¹⁴ and with the availability of treatment strategies for adenoviral infection,^{20–24} it is important to recognize that pancreatitis may signify dissemination of adenoviral infection.

Patients and methods

In the period between January 2001 and December 2004, we performed 36 myeloablative autologous and 59 allogeneic transplants in our institution. We defined pancreatitis as a serum lipase and amylase above the normal range. The records of these 95 children were reviewed for evidence of pancreatitis. We identified five children with a raised amylase and lipase. As drugs are commonly associated with pancreatitis, the drugs given 30 days before the onset of pancreatitis in these five patients were reviewed. These drugs were divided into one of three groups:²⁵ in the first group, the drug association seems to be definite, usually from carefully documented studies showing appearance of pancreatitis during treatment with the drug, disappearing when withdrawn and often appearing again when drug was reintroduced. In the second group, an association with pancreatitis is thought probably to exist but reports do not fulfil all the criteria for group 1 and drugs in the third group are thought either not to cause pancreatitis or if proposed, the evidence is inadequate. One of the five patients had drug-induced pancreatitis,²⁶ and, in the other four patients, it was unlikely their pancreatitis was due to any drugs given; these patients had adenovirus infection. We report the first case series of four children who had pancreatitis associated with the presence of adenovirus infection after BMT.

Viral studies

Monitoring of patients was consistent throughout the period of study. Patients were monitored for cytomegalovirus (CMV) weekly until at least day 120 (or until immunosuppressive therapy had ceased and CD4 recovery was documented) by CMV antigenaemia by pp65. Weekly specimens of urine and stool for viral culture were obtained

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routinely from all in-patients undergoing BMT. Follow-up samples as out-patients were only obtained from patients who had a virus previously isolated or with onset of new symptoms. Other specimens were obtained depending on clinical signs and were obtained from the patients manifesting signs of pancreatitis. Specimens for virological examination were nasopharyngeal secretions, faeces or urine. All specimens were transported immediately to the laboratory on ice. Polymerase chain reaction (PCR)-based methods for detecting virus, such as Adenovirus PCR, were not used throughout this time.

The specimens were diluted 1:10 in viral transport medium to a volume of 3 ml mixed by vortex and frozen at -20°C overnight. The following morning the specimen was thawed at 37°C in a water bath and centrifuged at 800 g for 20 min at 4°C . Supernatant from the centrifuged specimen (200 μl) was inoculated onto R-Mix cells (Diagnostic Hybrids, Athens, OH, USA) or diploid fibroblast (MRC-5; Biowhittaker, Walkersville, MD, USA) cell culture tubes and incubated at 37°C . The R-Mix cells were labelled on day 3 with adenovirus confirmed by indirect immunofluorescent-antibody technique with monoclonal antibodies specific for adenoviruses (Barteles, Washington, DC, USA), whereas the MRC-5 cultures were inspected three times weekly for cytopathic effect and adenovirus was confirmed by indirect immunofluorescent-antibody technique as described above. No analysis of adenovirus subtype was performed.

Over the course of the study period, 19 (20%) out of 95 patients in the study had adenovirus isolated. In 15 of these patients, adenovirus was isolated in the stool, four patients went on to develop pancreatitis and are described here. For each patient, any symptoms that could be related to adenovirus infection at the time of isolation are reported.

Patient 1. A 3-year-old boy with T-cell acute lymphoblastic leukaemia (ALL) received a 10/10 HLA-matched, partially T-cell depleted, unrelated peripheral blood stem cell (PBSC) transplant with total body irradiation on days -8 to -5 (total dose = 1320 cGy) and melphalan 140 mg/m^2 only once on day -2 (total dose = 140 mg/m^2) and antithymocyte globulin (ATG) 30 $\text{mg}/\text{kg}/\text{day}$ on days -7 , -5 and -2 (total dose = 90 mg/kg), as he failed to achieve first remission with standard ALL induction therapy. GVHD prophylaxis was with cyclosporine. Engraftment (first day of 3 consecutive days to absolute neutrophil count $>0.5 \times 10^9/\text{l}$) was achieved on day 11.

On day 27 post transplant, adenovirus was detected by culture in faeces in association with profuse watery diarrhoea. Cidofovir at 3 $\text{mg}/\text{kg}/\text{week}$ was started with hydration and probenecid at the time of administration. Immunosuppression with cyclosporine and prednisolone 2 $\text{mg}/\text{kg}/\text{day}$ was continued owing to on-going GVHD of skin and gastrointestinal tract (GIT). This regimen was tolerated well. The last adenovirus-positive stool was detected on day 30 post transplant and diarrhoea transiently improved. Adenovirus surveillance continued with weekly viral stool culture, which remained negative. In the 18 months after BMT, his major problems were related to GVHD, recurrent infections with poor graft function.

Table 1 Amylase and lipase levels with imaging performed

Patient no.	Peak amylase ^a	Peak lipase ^b	Imaging
1	327	2743	Normal – USS only
2	3324	12 239	Oedema of pancreas on CT
3 (1st episode)	519	1964	Oedema of pancreas on USS
(2nd episode)	215	3281	Normal
4	6680	5629	Normal – CT and USS

Abbreviations: CT = computer tomography of abdomen; USS = ultrasound scan of abdomen.

^aNormal range 20–85 U/l.

^bNormal range 114–286 U/l.

On 545th day post transplant, he developed central abdominal pain and vomiting with an associated raised serum amylase and lipase (see Table 1). Adenovirus was again identified by culture in the faeces. A diagnosis of acute pancreatitis was made. He was treated conservatively by being placed 'nil by mouth', and he received nutritional support with total parenteral nutrition (TPN) and opioid analgesia. The symptoms and serum markers of pancreatitis resolved over a 4-week period. The drugs given 30 days before the onset of pancreatitis can be seen in Table 2. He had GVHD of skin and GIT being treated with prednisolone 0.3 $\text{mg}/\text{kg}/\text{day}$ and mycophenolate mofetil (MMF) 250 $\text{mg}/\text{m}^2/\text{day}$. It was felt that GVHD was under control, and he was on a weaning regimen of prednisolone and MMF. He was lymphopenic, with a total CD3 count of $0.28 \times 10^9/\text{l}$ just before the development of pancreatitis. He did not receive any further specific therapy for adenovirus but continued to have his immunosuppression weaned. No further episodes of adenovirus infection or acute pancreatitis occurred. He died on day 859 post transplant of complications related to bacterial infection and on-going chronic GVHD but had no further episodes of pancreatitis or adenovirus infection.

Patient 2. A 5-year-old girl with secondary acute myeloid leukaemia French-American-British M4, after treatment for pelvic embryonal rhabdomyosarcoma, received a 10/10 HLA-matched, partially T-cell depleted, unrelated BMT with busulphan 150 $\text{mg}/\text{m}^2/\text{day}$ orally once a day on days -7 to -4 (total dose = 600 mg/m^2), melphalan 70 $\text{mg}/\text{m}^2/\text{day}$ intravenously once a day on days -3 to -1 (total dose = 210 mg/m^2) and ATG 30 $\text{mg}/\text{kg}/\text{day}$ on days -8 , -6 and -4 (total dose = 90 mg/kg). GVHD prophylaxis was with cyclosporine. Engraftment with neutrophils was achieved on day 10.

On day 18 post transplant, adenovirus was detected by culture in the faeces. This was associated with profuse watery diarrhoea, abdominal distension and hepatomegaly. With symptoms suggesting possible adenovirus dissemination, and with concurrent treatment with prednisolone and cyclosporine for GVHD, cidofovir was started at 5 $\text{mg}/\text{kg}/\text{week}$ with hydration and probenecid at the time of administration. The symptoms resolved with the last isolate of adenovirus in stool being on day 28 post transplant. Adenovirus surveillance continued with weekly stool viral

Table 2 Drugs received within one month before onset of pancreatitis

Patient no.	Drugs causing pancreatitis		
	Definite ^a	Not definite ^b	Unlikely
1	Trimethoprim/sulphamethoxazole Frusemide Paracetamol Prednisolone	GCSF Ondansetron Lisinopril Loperamide Ranitidine	Amikacin Fluconazole Gentamicin Meropenem Mycophenolate mofetil Ticacillin/clavulanic acid Valaciclovir Vancomycin
2	Trimethoprim/sulphamethoxazole Frusemide Prednisolone Cyclosporine Paracetamol	Itraconazole Metronidazole Omeprazole Ondansetron	Buscopan Cephalothin Gentamicin Metoclopramide Nifedipine Ticarcillin/clavulanic acid
3	Trimethoprim/sulphamethoxazole Prednisolone Paracetamol	Ciprofloxacin GCSF Liposomal Amphotericin Ondansetron Omeprazole Ranitidine Tacrolimus	Amoxicillin and clavulanic acid Cephalothin Cidofovir Probenecid Teicoplanin Ticarcillin/clavulanic acid
4	Trimethoprim/sulphamethoxazole Frusemide	<i>Cis</i> -retinoic acid Ondansetron Omeprazole	Cephalothin Cidofovir Fluconazole Gentamicin Probenecid Ticacillin/clavulanic acid

Abbreviations: GCSF = granulocyte colony-stimulating factor; TPN = total parenteral nutrition.

^aWell recognized with documented studies showing appearance during treatment with the drug, disappearing when withdrawn.

^bProbably does exist but does not fulfil the criteria for definite.

culture, which remained negative. After this time, her main problems were related to GVHD and infection.

On day 115 post transplant, she was admitted to the intensive care unit with acute onset central abdominal pain, hypotension and anaemia in association with a raised amylase and lipase (see Table 1). A diagnosis of acute haemorrhagic pancreatitis was made and she was treated conservatively by being placed 'nil by mouth', and she received TPN and opioid analgesia. A computed tomography (CT) scan of abdomen showed an oedematous pancreas consistent with pancreatitis. Her pancreatitis resolved rapidly. No adenovirus was isolated at this time. The drugs given 30 days before can be seen in Table 2. Her GVHD at the time of pancreatitis was under control, although she was receiving treatment with 2 mg/kg prednisolone and cyclosporine. She had no further episodes of pancreatitis or adenovirus and remains well.

Patient 3. A 10-year-old boy with T-cell non-Hodgkin's lymphoma in third remission received a 6/6 HLA-matched T-cell depleted, related PBSC transplant with total body irradiation (1320 cGy) and melphalan (total dose = 140 mg/m²) conditioning. GVHD prophylaxis was with cyclosporine and *in vitro* T-cell depletion. Engraftment with neutrophils was achieved on day 17. He had Grade 2 GVHD of skin and gut.

On day 114 post transplant, he first had adenovirus detected by culture in faeces with associated fever and diarrhoea. At this time, he was on weaning doses of prednisolone and tacrolimus for GVHD. However, because of the continued immunosuppression on day 126, he started treatment with cidofovir 3 mg/kg/dose, including hydration and probenecid, which was subsequently changed to 1 mg/kg/dose three times per week owing to renal impairment. On day 155 post transplant, he had acute onset abdominal pain with vomiting with a raised serum amylase and lipase consistent with pancreatitis (see Table 1). A diagnosis of acute pancreatitis was made. An ultrasound showed a large echogenic pancreas. This resolved with conservative management by being placed 'nil by mouth', receiving TPN and opioid analgesia. A second episode of pancreatitis occurred on day 215 post transplant, with adenovirus isolated in the stools at the same time. Cidofovir was started at 1 mg/kg/dose three times a week. The last isolate of adenovirus was on day 225 after BMT. The pancreatitis resolved with conservative management as it had previously. He was lymphopenic throughout this time, with a total CD3 count of 0.15–0.34 × 10⁹/l through the two episodes of pancreatitis. No further adenovirus was isolated despite stools being examined by viral culture, and there were no further episodes of pancreatitis. During both episodes of pancreatitis, his GVHD was clinically felt to be under control. This

patient died on day 286 post transplant of a bacterial infection related to excision of an adenocarcinoma of the colon.

Patient 4. A 3-year-old boy with Stage 4 neuroblastoma who received an autologous transplant with conditioning as busulphan 150 mg/m² orally once a day from day -7 to -4 (total dose = 600 mg/m²) and melphalan 100 mg/m² intravenously only once on day -2 (total dose = 100 mg/m²).

On day 16 post transplant, he developed diarrhoea with adenovirus detected by culture in his faeces. The diarrhoea continued, so cidofovir 3 mg/kg/day once a week was started, with hydration and probenecid, and continued until resolution of diarrhoea on day 54 post transplant. A biopsy of the GIT suggested the presence of adenovirus inclusions. On day 174 post transplant, the patient was admitted with diarrhoea and abdominal pain and *Stenotrophomonas maltophilia* septicaemia with a raised amylase and lipase (see Table 1). A CT scan performed showed oedema around the pancreas consistent with pancreatitis. He was treated conservatively by being placed 'nil by mouth', and he received TPN and opioid analgesia. Adenovirus was not isolated in the stools at this time. He was not given any new drugs likely to cause pancreatitis (see Table 2). His pancreatitis resolved over a period of weeks. He had no further adenovirus isolates or episodes of pancreatitis and remained well until he relapsed with metastatic neuroblastoma 2.5 years after BMT.

Discussion

In a 4-year period, we performed 95 BMTs in our institution and five children had pancreatitis; four also had adenovirus infection and these children are reported here. The fifth patient's acute pancreatitis was related to the administration of tacrolimus.²⁶ It is our clinical practice to perform a serum amylase and lipase on all patients with abdominal pain, nausea and vomiting. Our incidence of 5.3% is consistent with other published studies of pancreatitis after BMT.^{27,28}

There are many reports of pancreatitis as a complication of BMT where finding the aetiology can be troublesome.²⁷⁻²⁹ This group of patients are at an increased risk of getting pancreatitis for many reasons: the intensive conditioning regimen associated with BMT; GVHD itself perhaps causes pancreatitis and further the drugs to treat it are known to cause pancreatitis; and even other drugs administered throughout the transplant period are known or suspected causes of pancreatitis. The prolonged period of immunosuppression post BMT also exposes patients to viral infections and one of the many viral infections causing pancreatitis is adenovirus.^{14,30}

Our four patients presented with the typical constellation of symptoms and signs of acute pancreatitis, with abdominal pain, nausea and vomiting associated with a rise in amylase and lipase.³⁰ In patient 1 and, after the second episode of pancreatitis, in patient 3, the imaging was normal. This does not contradict the diagnosis as it is recognized that the imaging of the pancreas, with ultrasound and/or CT, can be normal if the pancreatitis is

mild or imaging is performed early in the course of the disease.²⁷ Both these patients had the imaging performed within 72 h of their first symptoms.

All four patients had different diseases and received differing conditioning regimens before BMT. Patients 1, 2 and 3 had GVHD, Grade 2 or above. We felt that GVHD of the pancreas was unlikely, as, firstly, whether pancreatitis can be attributed to GVHD is not well described in the literature; secondly, they had not had a recent flare of GVHD and the dose of steroids was either weaning (patients 1 and 3) or had been on same dose for a period of time (patient 2) and, thirdly, case 4 was an autograft. Although all four patients were, in the 30 days before the first episode of pancreatitis, receiving medication that has previously been implicated in causing pancreatitis (see Table 2), they had all been on these medications for a long period of time. None of the patients were commenced on a medication that had a definite association with causing pancreatitis. No drug was withdrawn because it was suspected as being the cause of the pancreatitis. The established criterion for drug-induced pancreatitis²⁵ was not met by any patient. Based on documented T-cell counts, concurrent therapy or their time post BMT, all four patients were immunosuppressed at the time of adenovirus isolation and pancreatitis.

It is clear from the description of our cases that we cannot ascribe causality to the association of adenovirus infection and pancreatitis. However, all four patients had adenovirus isolated either at the time of pancreatitis or before the onset of pancreatitis. In patient 1, the pancreatitis was associated with further isolates of adenovirus in stool, with a long period without any isolates. Patient 2 had adenovirus isolated in stool 90 days before onset of pancreatitis. With patient 3, adenovirus was isolated 40 days before onset of symptoms of the first episode of pancreatitis but concurrently with the second episode of pancreatitis. Cidofovir was being administered to treat the first episode of adenovirus and was stopped 2 weeks before the pancreatitis. Cidofovir was restarted with the second episode of pancreatitis and after this time, there were no further isolates of adenovirus. Patient 4 had pancreatitis 120 days after adenovirus infection with no other cause isolated. There may be a significant interval between isolation of adenovirus and development of symptoms of pancreatitis as reported previously.¹⁴ Furthermore, there are animal models where adenovirus can cause experimental pancreatitis.³¹

It is difficult to be certain of the aetiology of pancreatitis in any patient after BMT, whether it is secondary to BMT, GVHD, drugs or viruses. We do know that dissemination of adenovirus is a significant cause of mortality after transplantation and treatment with cidofovir may well be useful.^{20,22,23} The co-occurrence of adenovirus infection and pancreatitis in our patients has led to us postulating that the adenovirus may have a role in the development of the pancreatitis. It is our experience in Australia and New Zealand that many BMT centres, particularly adult, do not process stool samples in such a way that adenovirus could be isolated. It is possible that development of pancreatitis may herald dissemination of infection in a patient who is known to carry adenovirus post BMT. We would also

recommend a low threshold for investigating a patient for pancreatitis who has any abdominal symptoms post BMT, and include specific stool culture for viral isolation, if they are not already known to excrete adenovirus.

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