Bone Marrow Transplantation, (1999) 23, 511–513

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Case report

Pulmonary enterovirus infections in stem cell transplant recipients

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Summary:

In recent years, it has been recognised that the community respiratory viruses are a frequent cause of upper and lower respiratory tract infections in immunocompromised hosts such as bone marrow transplant recipients. By contrast, infections by non-polio enteroviruses have rarely been reported after stem cell transplantation. We present four cases of acute respiratory illness with enterovirus isolated as the sole pathogen from bronchoalveolar lavage. All four patients developed pneumonia and three died of progressive pneumonia, which reflects the severity of this complication. We conclude that enteroviral pulmonary infections may be a cause of severe pneumonia in immunocompromised hosts.
Keywords: enterovirus; pulmonary infection; immunocompromised host

Pneumonia is a frequent infectious complication in patients with hematologic malignancies, particularly following stem cell transplantation (SCT). Most viral pneumonias in these patients have been traditionally associated with herpes viruses. In recent years, however, an increasing number of reports have shown the importance of upper and lower respiratory tract infections in SCT recipients and other immunocompromised hosts caused by community respiratory viruses, mainly respiratory syncytial virus, influenza A and B, parainfluenza, adenovirus and picornaviruses.[1–6] The human picornaviruses (family *Picornaviridae*) which cause respiratory infections include rhinoviruses and enteroviruses, which in turn are classified into polioviruses, coxsackieviruses A and B, echoviruses and enterovirus 68–71. Infections by non-polio enteroviruses have rarely been reported in SCT recipients. Herein, we describe the presentation and clinical course of four highly immunocompromised SCT recipients with an acute respiratory illness who had enterovirus isolated from the bronchoalveolar lavage (BAL).

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Received 9 June 1998; accepted 18 October 1998

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One hundred and forty-four patients with hematologic malignancies received an allogeneic SCT and 414 patients received an autologous SCT between January 1990 and November 1997 at our institution. During this period, 190 BAL were performed in SCT recipients with an acute lower respiratory illness. All specimens were submitted for virological studies including antigen detection of respiratory viruses and tissue culture inoculation for cytomegalovirus, herpes simplex virus, enteroviruses and conventional respiratory viruses. An enterovirus was isolated as the sole pathogen in the BAL from four patients, whose characteristics are summarized in Table 1.

UPN 463

A 6-year-old male underwent an autologous bone marrow transplant (ABMT) for acute lymphocytic leukemia (ALL) in second complete remission (CR). The leukemia relapsed 9 months post-ABMT, and he received salvage chemotherapy with ICE (idarubicin, standard-dose cytarabine and etoposide). On day 20 of chemotherapy, neutropenic fever developed and empiric treatment with ceftazidime and amikacin was begun. Fever persisted and on day 24 he developed a nonproductive cough with a normal chest X-ray, and on subsequent days vancomycin and liposomal amphotericin B were added. The patient did not defervesce and by day 33 his chest X-ray showed an alveolar infiltrate in the left upper lobe. A BAL was performed which grew only a non-polio enterovirus. Following neutrophil recovery the fever abated and the respiratory symptoms slowly improved.

UPN 666

A 52-year-old male underwent an allogeneic peripheral blood SCT (PBSCT) from an HLA-identical sister for mantle cell lymphoma in refractory relapse. The post-PBSCT course was uneventful, but the disease recurred in blastic phase on day +106. Cyclosporine (CsA) was discontinued and salvage chemotherapy with ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin) was given, followed by infusion of PBSC from the same donor. Twenty-five days after the second ESHAP he developed grade II acute GVHD, with complete response to steroids plus CsA. On day 50 after the second ESHAP he developed

Table 1 Patient characteristitics at SCT

UPN	*Age/Sex (year)*	*Underlying disease/stage*	*Conditioning regimen*	*Type of SCT*	*Result of SCT*	*Last treatment prior to infection*	*Day post-SCT of infection*	*ANC ($\times 10^9$/l)*	*Chest X-ray*	*Outcome*
463	6/M	B-lineage ALL/2nd CR	cyclophosphamide + TBI	ABMT	Relapse ALL day + 270	Day 20 post-salvage chemotherapy	+360	0.1	alveolar infiltrate in left upper lobe	Cured
666	52/M	MCL/Refr Rel	chlorambucil + cyclophosphamide + TBI	AlloPBSCT-TCD HLA-id sib	Relapse MCL day +106	Day 50 post-salvage chemotherapy followed by infusion of PBSC	+160	3.54	patched alveolar bilateral infiltrates	Died
759	13/M	T-lineage ALL/2nd CR	cyclophosphamide + TBI	ABMT	Relapse ALL day +90	Day 23 post-salvage chemotherapy	+120	0.3	alveolar infiltrate in right lower lobe	Died ARDS at autopsy
811	5/M	B-lineage ALL/Rel after syngeneic BMT	melphalan + busulphan + ATG	Unrelated AlloCBT	died of infection	Day +37 AlloCBT	+37	0.12	Bilateral alveolar-interstitial infiltrates	Died ARDS at autopsy

SCT = stem cell transplant; M =male; ALL = acute lymphocytic leukemia; MCL = mantle cell lymphoma; CR = complete remission; Refr Rel = refractory relapse; HLA-id sib = HLA-identical sibling; AlloPBSCT-TCD = allogeneic peripheral blood stem cell transplantation, T cell depleted; ABMT = autologous bone marrow transplant; AlloCBT = allogeneic cord blood transplantation; TBI = total body irradiation; ATG = antithymocyte globulin; ANC = absolute neutrophil count; ARDS = adult respiratory distress syndrome.

fever and a nonproductive cough. Chest X-ray showed a bilateral alveolar infiltrate, and empiric treatment with imipenem was begun. Within 48 h (day 52) fever persisted with respiratory deterioration, liposomal amphotericin B was added and a BAL was performed. On day 58 the patient developed overt respiratory failure and i.v. steroids plus ganciclovir were added. The BAL was reported positive for a non-polio enterovirus. Despite aggressive supportive management, the patient's respiratory status further worsened and he died on day 64. Consent for a post-mortem study was not given.

UPN 759

A 13-year-old male received an ABMT for ALL in second CR. The disease recurred 3 months after SCT and salvage chemotherapy with ICE was given. On day 23 of chemotherapy he developed neutropenic fever and was treated with ceftazidime plus amikacin for *Escherichia coli* bacteremia. Fever persisted over the following days with no further positive blood cultures, and within 2 days he developed respiratory symptoms with a right lower lobe alveolar infiltrate on chest X-ray. Liposomal amphotericin B was added and a first BAL was performed. Two days later he required intubation with mechanical ventilation and a second BAL was performed. Both BALs were later reported positive for a non-polio enterovirus. The patient died 2 days later with multi-organ failure and post-mortem examination revealed diffuse pulmonary lesions consistent with adult respiratory distress syndrome (ARDS).

UPN 811

A 5-year-old male underwent a syngeneic BMT for ALL in second CR. The disease recurred within 6 months, and after achieving a third CR he underwent an unrelated cord blood transplant 9 months from the first BMT. CsA and steroids were given as GVHD prophylaxis. On day +18, grade I acute GVHD appeared with complete response to an increase in the dose of i.v. steroids. On day +37 he developed recurrent neutropenic fever which was treated with ceftazidime plus amikacin. Blood culture yielded *Pseudomonas aeruginosa* and viridans streptococci. The patient was on prophylactic liposomal amphotericin B and vancomycin was added on day +39. That same day bilateral alveolar infiltrates were first noted and the patient developed frank respiratory failure within 24 h, requiring intubation with mechanical ventilation; a BAL was performed which was later reported positive for a non-polio enterovirus. Despite aggressive supportive management the patient died 6 days later from multi-organ failure. Post-mortem examination revealed only pulmonary changes consistent with ARDS.

Discussion

Enteroviruses are frequent human pathogens. In immunocompetent hosts their main clinical presentations are a common cold-like or flu-like syndrome and they may often be asymptomatic. Mild respiratory symptoms usually predominate. Additionally, enteroviruses are a leading cause of viral meningitis in children and myocarditis in all age groups. Enteroviruses spread from person to person. The usual mode of transmission is fecal–oral and studies of respiratory infection induced by certain types of enteroviruses in adult volunteers have shown that intranasal or aerosol administration more effectively induces respiratory infection.[7] Isolation of enteroviruses requires cellular cultures. Once identified, serotyping is cumbersome since more than 68 serotypes have been described to date and only reference laboratories can type all known serotypes. These difficulties may explain why enteroviral diagnostic techniques are unavailable on a routine basis in most microbiology laboratories and why these viruses have rarely been reported as causing infections in immunocompromised hosts. New highly sensitive PCR-based methods are being developed, but at present these diagnostic techniques are available only in research laboratories.[8]

There have been few previous reports describing

enterovirus infections in immunocompromised cancer patients in general and SCT recipients in particular. Two BMT recipients had an enterovirus (non-polio enterovirus in one and echovirus 11 in another) isolated from various organs in the setting of fatal pericarditis and pneumonitis.[9,10] In a prospective study of infectious gastroenteritis in BMT recipients, a coxsackievirus was isolated in the stools of four patients, all of whom died from this complication;[11] these same investigators reported an epidemic of coxsackie A1 gastroenteritis affecting seven patients with six fatalities.[12] Surprisingly, there have been no other reports of lower gastrointestinal infections by these viruses, and in immunocompetent hosts enteroviruses do not produce gastroenteritis. There have also been only few reports of acute lower respiratory tract infections by picornaviruses in hematopoietic SCT recipients, with most cases leading to severe respiratory failure and death. However, 90% of the isolates were rhinoviruses and only 10% were due to non-polio enteroviruses.[3,4] Some enteroviral pneumonias appear to be preceded by upper respiratory tract symptoms, but this sequence of events is not as apparent as with other community respiratory viruses such as rhinoviruses, parainfluenza viruses or respiratory syncytial virus.[4] As with other viral pneumonias, the exact implication of the isolation of an enterovirus from BAL and the fatal pulmonary infection is sometimes unclear, since post-mortem studies may be unavailable, show non-specific findings, or another pathogen (usually fungal or bacterial) may be identified. In our cases, however, only one patient (UPN 811) had concomitant infections which could otherwise explain the development of ARDS, namely *Pseudomonas aeruginosa* and viridans streptococci bacteremia.

In conclusion, the clinical course of these four patients reflects the severity of this complication. Enterovirus infection may be an additional cause of pneumonia in severely immunocompromised hosts. Larger patient series will be required to confirm this observation and to identify possible epidemiologic or clinical features.

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