**Bone Marrow Transplantation, (1998) 21,** 301–303


# Case report

# Fatal cytomegalovirus interstitial pneumonia following autologous peripheral blood stem cell transplantation

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**Summary:**

**A 52-year-old Japanese woman suffering from AML (FAB classification M4) in her first remission received an autologous peripheral blood stem cell transplant (APBSCT). She was seropositive for CMV prior to APBSCT. Her post-APBSCT course was complicated with CMV-associated disease and hemophagocytic syndrome. Finally, CMV interstitial pneumonia developed and death ensued. Even after APBSCT, there can be a short period of immune deficiency resembling that occurring following allogeneic or autologous BMT. CMV infection must be considered in the differential diagnosis in cases of unexplained fever or pneumonia following APBSCT.**

**Keywords:** cytomegalovirus; interstitial pneumonia; peripheral blood stem cell transplantation

Autologous peripheral blood stem cell transplantation (APBSCT) has been used in the treatment of hematologic malignancies.[1] Compared to BMT, APBSCT results in rapid hematopoietic recovery which reduces the morbidity and mortality from bacterial and/or fungal infectious complications.[2] However, reports about viral infections following APBSCT are very few. Recently, Sakuma *et al*[3] reported that there were no cases of cytomegalovirus (CMV)-associated disease among their 105 patients who had received APBSCT. We report the case of a Japanese woman who received APBSCT and subsequently developed fatal CMV interstitial pneumonia (IP).

## Case report

A 52-year-old Japanese woman was referred to our hospital because of a syncopal attack in May 1996. Her hemoglobin was 89 g/l, white blood cell count $177.2 \times 10^9$/l (77% blasts), and platelet count $41 \times 10^9$/l. A bone marrow aspirate showed a proliferation of blasts which were positive for myeloperoxidase and fluoride-inhibitable nonspecific esterase. AML (FAB classification M4) was diagnosed. She was treated with idarubicin 12 mg/m$^2$ once daily i.v. for 4 days, and Ara-C 100 mg/m$^2$ by continuous i.v. infusion over 24 h for 10 consecutive days. With this induction therapy, she achieved CR. The first consolidation therapy comprised intermediate-dose Ara-C (500 mg/m$^2$ twice daily i.v. for 6 consecutive days) combined with mitoxantrone (7 mg/m$^2$ i.v. for 3 consecutive days), while the second comprised intermediate-dose Ara-C combined with etoposide (100 mg/m$^2$ i.v. for 5 consecutive days). During hematopoietic recovery after the second course of consolidation therapy, PBMC were harvested by continuous flow leukapheresis and cryopreserved. The total number of PBMC collected was $1.1 \times 10^9$/kg, which contained $0.44 \times 10^5$/kg of colony-forming unit granulocyte–macrophages, $2.8 \times 10^6$/kg of CD34$^+$ cells, and $0.4 \times 10^9$/kg of CD3$^+$ cells. She was seropositive for CMV prior to APBSCT (CF ×32, IgG (EIA index) 89.1 (+), IgM 0.18 (–)). The patient received her APBSCT on 19 September 1996. The pre-transplant conditioning regimen (G-CSF combined BEA) consisted of rhG-CSF (Kirin, Tokyo, Japan) administered at a dose of 5 $\mu$g/kg i.v. daily on days –14 to –8, 10 $\mu$g/kg on days –7 and –6, and 20 $\mu$g/kg on days –5 and –4, Ara-C 100 mg/m$^2$ by continuous i.v. over 24 h daily on days –12 to –6, busulfan 4 mg/kg p.o. in divided doses daily on day –9 to –6, etoposide 20 mg/kg i.v. daily on days –5 and –4, and Ara-C 3 g/m$^2$ twice daily i.v. on days –3 and –2.[4] Acyclovir was administered at a dose of 5 mg/kg i.v. daily on days +1 to +14, and anti-CMV hyperimmune globulin 100 mg/kg on days +1 and +2. On day +6 fever developed which did not resolve. Nevertheless, her granulocyte count exceeded $0.5 \times 10^9$/l on day +11. Bone marrow aspiration on day +25 showed marked hemophagocytosis. Hemophagocytic syndrome was diagnosed and prednisolone 1 mg/kg i.v. daily was administered. She became afebrile temporarily, but then fever recurred. On day +35, CMV antigenemia assay revealed strong positivity ($199/5 \times 10^4$ WBC).[5] CMV-associated diseas with CMV-associated hemophagocytic syndrome was diagnosed and gancyclovir (5 mg/kg twice daily i.v.) and anti-CMV hyperimmune globulin 200 mg/kg once a week were administered. However, gancyclovir was withdrawn on day +48

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Received 3 June 1997; accepted 11 September 1997

because of myelotoxicity (white blood cell count $0.3 \times 10^9$/l, and platelet count $6 \times 10^9$/l on day +48). On day +56, hemorrhagic cystitis developed and CMV was isolated from the urine. Again, the CMV antigenemia assay revealed strong positivity ($16/5 \times 10^4$ WBC), and foscarnet (60 mg/kg three times daily i.v.) was administered.[6] With foscarnet treatment, CMV-antigenemia disappeared, and administration of foscarnet was terminated on day +84. Due to recurrence of CMV-associated hemophagocytic syndrome (day +112 CMV-antigenemia $2/5 \times 10^4$ WBC), granulocytopenia developed and foscarnet was re-administered on day +116. With this treatment, the granulocytopenia and CMV antigenemia resolved. The administration of foscarnet was again terminated on day +140. On day +158, IP developed (Figure 1) and progressive respiratory failure occurred. Bronchoalveolar lavage revealed inclusion bodies and CMV IP was diagnosed. Despite treatment with foscarnet and anti-CMV hyperimmune globulin, she died of respiratory failure on day +171 (Figure 2).

## Discussion

APBSCT has been used increasingly because it results in rapid hematopoietic recovery and allows rapid immune reconstitution. Compared to allogeneic BMT, serious infectious complications are much less likely to develop after APBSCT. CMV-associated disease is a serious complication following allogeneic stem cell transplantation.[5,7] On the other hand, CMV-associated disease is reported as not occurring after APBSCT by Sakuma *et al*.[3]

This is our first case of fatal CMV-associated disease following APBSCT, our hospitals having undertaken 67 cases of APBSCT for AML from 1989 to 1996. Sakuma *et al*[3] reported that none of 17 pediatric APBSCT patients were positive for CMV antigenemia at day +35, although four of them were CMV-seronegative prior to APBSCT. In contrast, Boeckh *et al*[8] reported that among 41 CMV-seropositive APBSCT patients, 15 were CMV-antigenemia positive at day +16 to +61, and one patient developed CMV retinitis on day +130. There were differences in patient ages and CMV seropositivity: most patients of Sakuma *et al* were pediatric, and of Boeckh *et al* were adult. Peusser *et al*[9] reported that positive pre-transplant CMV serology was the most significant risk factor for CMV infection in the setting of ABMT. The higher incidence of CMV antigenemia and CMV-associated disease in the series of Boeckh *et al* compared to that of Sakuma *et al* seems to be influenced by older ages and higher CMV seropositivity. Even after APBSCT, there can be a short period of immune deficiency resembling that occurring after allogeneic or autologous BMT.[10] Moreover, fatal CMV-associated disease has been reported following ABMT.[8]

We consider that the possibility of serious CMV-associated disease developing after APBSCT should not be discounted. We cannot elucidate the reason why our patient suffered from refractory CMV-associated disease, although prednisolone administered for the treatment of hemophago-

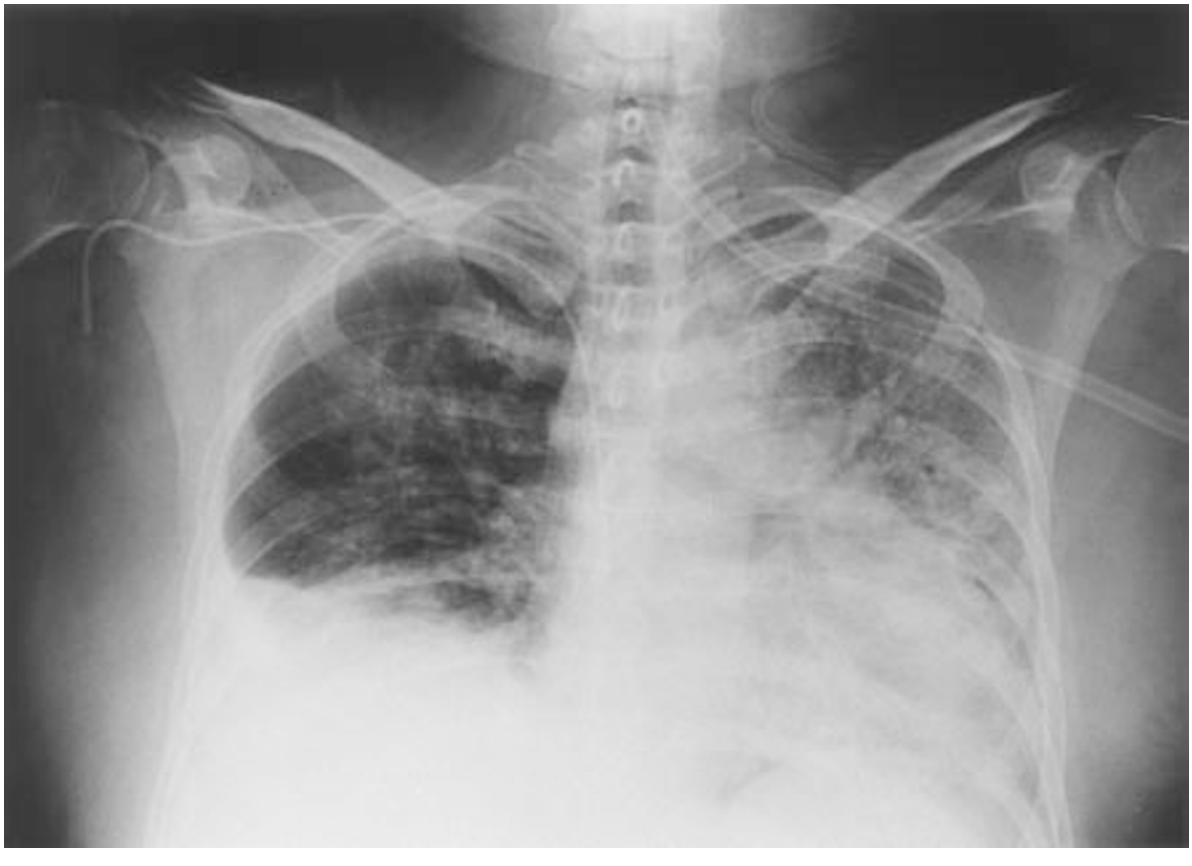

**Figure 1** Chest radiograph on day +160. The radiograph shows bilateral diffuse interstitial infiltrates.

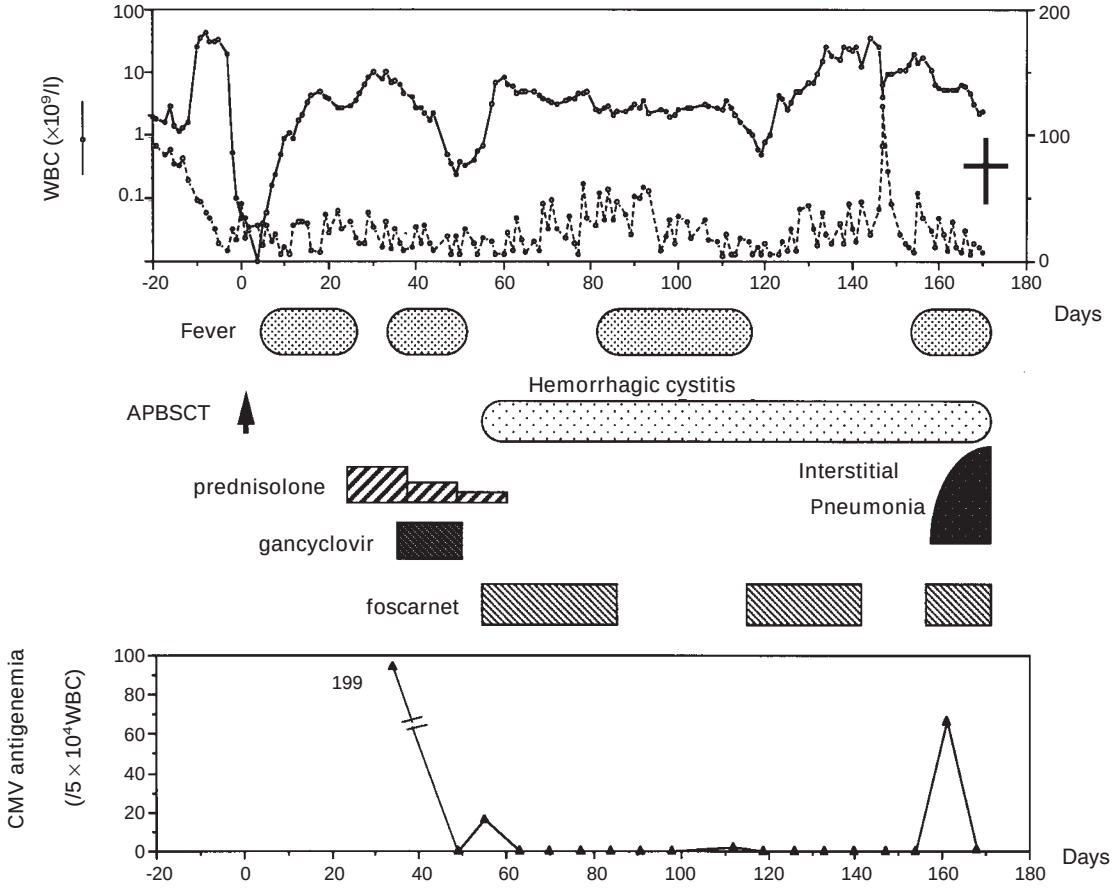


**Figure 2** Clinical course following APBSCT. After APBSCT, the patient suffered from CMV-associated disease, hemophagocytic syndrome, and hemorrhagic cystitis. Finally, CMV-IP developed and this proved fatal.

cytic syndrome may have affected the clinical course of her CMV infection.

In conclusion, even after APBSCT, CMV infection must be considered in the differential diagnosis in cases of unexplained fever and/or pneumonia especially in pre-transplant CMV-seropositive patients.

## Acknowledgements

The English in this manuscript was revised by Miss K Miller (Royal English Language Centre, Fukuoka, Japan).

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