Leading Article

Cytomegalovirus infection complicating immunosuppressive treatment

P.D. Griffiths

The Royal Free Hospital, Pond Street, London NW3 2QG, UK.

Two case reports in this issue of the *Journal* describe remarkably similar clinical presentations. The patients (a 37 year old woman¹ with systemic lupus erythematosus and a 49 year old man² with glomerulonephritis and pulmonary haemorrhage) presented with lung involvement which improved after immunosuppressive therapy was instituted. The patients were maintained on lower doses of immunosuppressives and remained stable. Once their condition was under control, episodes of severe haemoptysis occurred four weeks and six weeks after initial presentation. Investigation of both patients led to lung biopsy which revealed inclusion bodies within the lung suggestive of cytomegalovirus (CMV) infection. One patient survived while the other died. The authors discuss whether the immunosuppression given might have reactivated CMV or whether the virus was transmitted by blood transfusion. They also discuss the pathogenesis of CMV infection of the lung.

Cytomegalovirus is a common infectious agent which is well adapted to hosts with normal immune responses. However, in immunosuppressed patients, latent virus can reactivate to lead to dissemination of infection and ultimately life-threatening disease. Such reactivations are the usual means by which CMV affects bone marrow transplant^{3,4} and acquired immune deficiency syndrome (AIDS) patients⁵ in whom pre-existing immunity confers little protection. In renal transplant patients, most reactivations of virus are asymptomatic while primary infections (transmitted with the donor kidney) are frequently life-threatening.⁶ Re-infection of patients with pre-existing antibody also occurs⁷ and disease can develop in a proportion. The virus can also be transmitted by blood transfusion and the serological status of the donor (seropositive) and of the recipient (seronegative) represent

markers of susceptibility to CMV spread by blood transfusion.⁸ The pathogenesis of the various clinical conditions caused by CMV is not completely understood. Involvement of the retina and gastrointestinal tract for example, appears to be mediated by active virus replication. In contrast, CMV can be detected readily in urine and saliva, without the accompaniment of symptoms.^{3,9-11} In the mouse model of CMV, the development of CMV pneumonitis requires a host immune response which can be suppressed by continued administration of cyclophosphamide¹² while the presence of graft versus host disease¹³ can turn an asymptomatic CMV infection into one with fatal outcome.

What lessons can be learned from these case reports which could ultimately benefit patients? Since CMV is the single commonest cause of death in bone marrow transplant patients¹⁴ and is a major cause of mortality and morbidity in renal transplant patients,^{15,16} physicians caring for such individuals should already be following standard protocols to detect this virus. Those caring for other groups of immunosuppressed patients may be stimulated by the two case reports to follow such guidelines, the principles of which are straightforward. First, when a patient presents with a clinical condition which may require therapeutic immunosuppression, his antibody status to CMV should be determined. The absence of antibody indicates that he is seronegative and so not infected with this virus and every attempt should be made to give him only blood products which have been shown to lack antibodies to CMV. The presence of antibody within the patient does not indicate immunity in the protective sense but is a marker for latent CMV infection which may reactivate under the influence of immunosuppressive drugs.¹⁵ Second, once immunosuppression has been administered, serology has no further diagnostic role to play since it is absurd to assume that such patients will be able to mount appropriate immune

Correspondence: P.D. Griffiths, M.D., B.Sc., M.R.C.Path.
Received: 12 August 1987

responses rapidly enough to permit changes in clinical management.³ Furthermore, sensitive serological assays detect CMV antibody passively acquired from blood donors which only confuses the picture further.³ Third, diagnosis should therefore be made exclusively by detection of virus. This should preferably be done by rapid methods using monoclonal antibodies which bypass the slow replicative cycle of CMV so that results can be available within 24 hours.¹⁷⁻¹⁹ Fourth, clinicians should not wait until the patient becomes febrile and ill before taking specimens; routine samples of urine, saliva and blood should be collected weekly while the patient is intensively immunosuppressed. Fifth, if the patient develops symptoms which might be due to an opportunistic agent, then invasive techniques should be considered at the earliest opportunity. For example, the use of rapid techniques can again diagnose CMV infection of the lung within 24 hours if bronchoalveolar lavage fluid is obtained.^{17,20} The use of such a relatively low risk technique as fiberoptic bronchoscopy is of course preferable to formal biopsy of the lung especially since standard histological methods detect only one in six samples which contain CMV by culture methods²¹ and because similar inclusion

bodies may be induced by viruses other than CMV.

By following such guidelines, clinicians will frequently detect CMV and will have the option of considering changes in management. Some infections, such as salivary or urinary excretion, are often not life-threatening but may prompt a judicious reduction in immunosuppressive treatment. However, detection of virus in the blood appears to be a marker of virus dissemination and so portends a poor prognosis.^{3,9-11,22} Thus, immunosuppressed patients with viraemia should have the dose of their immunosuppressive drugs reduced markedly even at the risk of exacerbating disease. Finally, if the patient has CMV infection of the lung, retina or gastrointestinal tract then a trial of one of the investigational anti-CMV drugs such as ganciclovir,²³ phosphonoformate²⁴ or intravenous immunoglobulin²⁵ may be warranted. However, the findings in the mouse model should caution against over-enthusiastic hopes for control of CMV disease where elements of the immune response are involved in pathogenesis. Perhaps some of the conflicting data will be resolved and better understood when a greater variety of immunosuppressed patients, such as those reported in this issue of the *Journal*, are more thoroughly investigated.

References

1. Kwong, Y.L., Wong, K.L., Kung, I.T.M., Chan, P.C.K. & Lam, W.K. Concomitant alveolar haemorrhage and cytomegalovirus infection in a patient with systemic lupus erythematosus. *Postgrad Med J* 1988, **64**: 56-59.
2. Chan, C.N., Lai, F.M., Lai, K.N. & Pang, J.A. Relapse of idiopathic pulmonary haemorrhage and glomerulonephritis associated with cytomegalovirus (CMV) infection. *Postgrad Med J* 1988, **64**: 52-55.
3. Panjwani, D.D., Ball, M.G., Berry, N.J. *et al.* Virological and serological diagnosis of cytomegalovirus infection in bone marrow allograft recipients. *J Med Virol* 1985, **16**: 357-365.
4. Meyers, J.D., Flournoy, N. & Thomas, E.D. Risk factors for cytomegalovirus infection after human marrow transplantation. *J Infect Dis* 1986, **153**: 478-488.
5. Quinnan, G.V. Jr., Masur, H., Rook, A.H. *et al.* Herpesvirus infections in the acquired immune deficiency syndrome. *JAMA* 1984, **252**: 72-77.
6. Glenn, J. Cytomegalovirus infections following renal transplantation. *Rev Infect Dis* 1981, **3**: 1151-1178.
7. Grundy, J.E., Super, M. & Griffiths, P.D. Reinfection of seropositive allograft recipients by cytomegalovirus from donor kidney. *Lancet* 1986, **i**: 159-160.
8. Yeager, A.S., Grumet, F.C., Haffleigh, E.B., Arvin, A.M., Bradley, J.S. & Prober, C.G. Prevention of transfusion-acquired cytomegalovirus infections in newborn infants *J Pediatr* 1981, **98**: 281-287.
9. Fiala, M., Payne, J.E., Berne, T.V. *et al.* Epidemiology of cytomegalovirus infection after transplantation and immunosuppression. *J Infect Dis* 1975, **132**: 421-433.
10. Betts, R.F., Freeman, R.B., Douglas, R.G. & Talley, T.E. Clinical manifestations of renal allograft derived primary cytomegalovirus infection. *Am J Dis Child* 1977, **131**: 759-763.
11. Pass, R.F., Whitley, R.J., Diethelm, A.G., Whelchel, J.D., Reynolds, D.W. & Alford, C.A. Cytomegalovirus infection in patients with renal transplants: potentiation by antithymocyte globulin and an incompatible graft. *J Infect Dis* 1980, **142**: 9-17.
12. Shanley, J.D., Pesanti, E.L. & Nugent, K.M. The pathogenesis of pneumonitis due to murine cytomegalovirus. *J Infect Dis* 1982, **146**: 388-396.
13. Grundy, J.E., Shanley, J.D. & Shearer, G.M. Augmentation of graft-versus-host reaction by cytomegalovirus infection resulting in interstitial pneumonitis. *Transplantation* 1985, **39**: 548-553.
14. Watson, J.G. Problems of infection after bone marrow transplantation. *J Clin Pathol* 1983, **36**: 683-692.
15. May, A.G., Betts, R.F., Freeman, R.B. & Andrus, C.H. An analysis of cytomegalovirus infection and HLA antigen matching on the outcome of renal transplantation. *Ann Surg* 1978, **187**: 110-117.

16. Andrus, C.H., Betts, R.F., May, A.G. & Freeman, R.B. Cytomegalovirus infection blocks the beneficial effect of pretransplant blood transfusion on renal allograft survival. *Transplantation* 1979, **28**: 451–456.
17. Griffiths, P.D., Panjwani, D.D., Stirk, P.R. *et al.* Rapid diagnosis of cytomegalovirus infection in immunocompromised patients by detection of early antigen fluorescent foci. *Lancet* 1984, **ii**: 1242–1245.
18. Alpert, G., Mazon, M.-C. & Plotkin, S. Rapid detection of human cytomegalovirus in the urine of humans. *J Infect Dis* 1985, **152**: 631–633.
19. Swenson, P.D. & Kaplan, M.H. Rapid detection of cytomegalovirus in cell culture by indirect immunoperoxidase staining with monoclonal antibody to an early nuclear antigen. *J Clin Microbiol* 1985, **21**: 669–673.
20. Springmeyer, S.C., Hackman, R.C., Holle, R. *et al.* Use of bronchoalveolar lavage to diagnose acute diffuse pneumonia in the immunocompromised host. *J Infect Dis* 1986, **154**: 604–610.
21. Smith, T.F., Holley, K.E., Keys, T.F. & Macasaet, F.F. Cytomegalovirus studies of autopsy tissue. *Am J Clin Pathol* 1975, **63**: 854–858.
22. Winston, D.J., Pollard, R.B., Ho, W.G. *et al.* Cytomegalovirus immune plasma in bone marrow transplant recipients. *Ann Intern Med* 1982, **97**: 11–18.
23. Collaborative DHPG Treatment Study Group. Treatment of serious cytomegalovirus infections with 9-(1,3-dihydroxy-2-propoxymethyl)guanine in patients with AIDS and other immunodeficiencies. *N Engl J Med* 1986, **314**: 801–805.
24. Editorial. Foscarnet. *Lancet* 1985, **ii**: 648–649.
25. Blacklock, H.A., Griffiths, P.D., Stirk, P.R. & Prentice, H.G. Successful treatment of cytomegalovirus pneumonitis after allogeneic bone marrow transplantation using high titre CMV immunoglobulin (Cytotect). *Exp Haematol* 1985, **13** Suppl 17): 76.