Cytomegalovirus pneumonia – a consequence of immunosuppression and pre-existing lung damage rather than immunopathology?

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Introduction

Cytomegalovirus pneumonia occurs in kidney, bone marrow, heart and heart-lung allograft recipients (1,2), but its existence in patients with the acquired immune deficiency syndrome (AIDS) is debated (3). Ganciclovir, a drug with in vitro activity against human cytomegalovirus (CMV), has failed to reduce the mortality when given as treatment for this pneumonia in bone marrow allograft recipients, despite a large reduction of virus titres in the lungs (4). This has led to a hypothesis that CMV pneumonia is an immunopathological condition (5). Notwithstanding, clinical and laboratory observations emphasize the importance of immunosuppression and pre-existing lung damage as antecedents of this disease. Viraemia and virus invasion of the lungs precede the pneumonia. An alternative hypothesis for the pathogenesis of CMV pneumonia is therefore proposed.

Clinical Observations

Immunosuppression is a pre-requisite for the development of CMV pneumonia (1). Among organ allograft recipients in general the incidence of CMV pneumonia correlates with the degree of immunosuppression. This incidence is increased in renal or bone marrow allograft recipients by administration of anti-thymocyte globulin (ATG) (6,7). CMV pneumonia is rare in renal patients given maintenance prednisolone only sparingly (8), and it may resolve following withdrawal of immunosuppression (9).

Among bone marrow allograft recipients, factors associated with an increased risk of CMV pneumonia include pre-transplant conditioning with ATG or total body irradiation (TBI) in patients with aplastic anaemia (1,7), pre-transplant conditioning with the cytotoxic drug bichloroethyl nitrosourea in patients with haematological malignancy (1), and post-transplant moderate to severe acute graft-versus-host disease (GVHD) (7). The incidence of all interstitial pneumonias [and perhaps of CMV pneumonias which comprise approximately 40% of interstitial pneumonias (7)] is increased by conditioning for marrow allografting using dose rates of TBI exceeding 0.04–0.06 Gy min\(^{-1}\) when methotrexate provides prophylaxis against GVHD (10,11). Doses of TBI greater than 6 Gy may also be associated with an increased risk of CMV pneumonia (12), though two studies have failed to document a link between the irradiation dose and the risk of all interstitial pneumonias (10,11). The importance of acute GVHD as a risk factor for CMV pneumonia in marrow allograft recipients is emphasized by the absence of both conditions in recipients of syngeneic grafts (13).

Laboratory Observations

Natural killer (non-T) and T-cell cytotoxic effector responses are an important component of the cellular immune response in the context of acquisition of and recovery from CMV infection in allograft recipients (14). Most currently available data relate to cytotoxic cell responses in the peripheral blood. The development of CMV-specific cytotoxic responses during infection correlates with a decreased likelihood of pneumonia and death in marrow allograft recipients, and a decreased likelihood of death in renal allograft recipients. Natural killer cell activity against CMV-infected cells is depressed in renal allograft recipients for the first 2 yr after transplantation, but rises to high levels following reductions in immunosuppressive therapy and in temporal association with resolution of CMV disease. In marrow allograft recipients, retention of natural cytotoxic activity against virus-infected target cells is associated with longer survival after CMV infection, and depression of such cytotoxic activity relative to normal controls accompanies the onset of acute GVHD. Depression of CMV-specific
cytotoxic T-cell responses in renal and bone marrow allograft recipients may follow high-dose methylprednisolone therapy, as in the former patients these responses are largely abolished 5–14 days after therapy, and in the latter patients the use of methylprednisolone and not merely the presence of GVHD correlates with reduced T-cell responses.

Natural killer cells mediating cytotoxic activity directed against virus-infected cells have been detected in bronchoalveolar lavage fluid collected from patients with CMV pneumonia (15). This cytotoxic activity was greater than that detected in the patients' peripheral blood, but its magnitude did not vary with the outcome of the pneumonia in the smaller number of patients studied (15).

CMV pneumonia and interstitial pneumonia associated with ionizing radiation or administration of cytotoxic drugs such as bichloroethylnitrosourea share several pathological features, including proliferation and desquamation of pneumocytes, accumulation of alveolar exudate, alveolar haemorrhage, fibrin deposition, interstitial edema, and formation of hyaline membranes (16-20). Functional damage to alveolar walls, perhaps in particular to pneumocytes, may be central to the pathogenesis of both CMV and interstitial pneumonias, in that reduction of the carbon monoxide diffusion capacity is almost always present (18). CMV replication (1,16). CMV probably replicates in pneumocytes as the damage to pneumocytes in the pneumonia. These observations suggest that pre-existing lung damage may be central to the pathogenesis of both CMV and interstitial pneumonias, in that reduction of the carbon monoxide diffusion capacity is almost always present (1,16). CMV probably replicates in pneumocytes as typical viral inclusions are present in these cells in patients with CMV pneumonia (18). CMV replication ultimately switches off host cell macromolecular synthesis (21), and this effect may underlie the functional damage to pneumocytes in the pneumonia. These observations suggest that pre-existing lung damage produced by irradiation or cytotoxic drugs could exacerbate lung damage consequent on pulmonary CMV infection.

Patients with CMV pneumonia have a high prevalence of preceding CMV viraemia (1,2,6). The reported failure to document viraemia in all patients with this pneumonia (7) may reflect the reduced sensitivity of virus isolation when blood samples are anticoagulated with heparin rather than Alsever's or citrate solution (22) and when leucocytes are separated by sedimentation rather than by density-gradient centrifugation (23). Subclinical pulmonary infection probably precedes overt pneumonia. Detection of virus in bronchoalveolar lavage fluid in asymptomatic bone marrow allograft recipients correlates with the subsequent development of pneumonia (24). Moreover, alveolar wall dysfunction manifest as a reduced carbon monoxide diffusion capacity is a virtually constant accompaniment of CMV infection in immunosuppressed renal transplant patients (25).

Proposed Pathogenesis of CMV Pneumonia

CMV reaches the lungs during an episode of viraemia. Two steps occur between the onset of viraemia and the onset of clinically apparent pneumonia. First, virus invasion of the lung parenchyma, in the form of infection of occasional pneumocytes, produces subclinical pulmonary infection manifest as virus shedding in bronchoalveolar secretions and perhaps resulting in an alveolar diffusion deficit. Second, virus replication and dissemination in the lung, mainly in pneumocytes, leads to clinically and radiologically apparent pneumonia. Functional damage to or destruction of pneumocytes is central to the development of CMV pneumonia, and reflects either the direct effects of infection of these cells on host cell macromolecular synthesis or their immune destruction by cytotoxic cells.

Immunosuppression promotes the development of CMV pneumonia by increasing the likelihood that viraemia will lead to pneumonia. The effects of immunosuppression and acute GVHD on the risk of this pneumonia are mediated by depression of specific cytotoxic T and non-T cell responses. Depression of these responses predisposes to the development of pneumonia by increasing the likelihood of either virus infection or of dissemination within the lung. The high prevalence of subclinical pneumonia in CMV-infected renal transplant patients who escape clinical pneumonia suggests that the second mechanism is the more important.

Radiotherapy and cytotoxic chemotherapy increase the risk of CMV pneumonia in immunosuppressed patients by reducing the extent of virus-induced damage of pneumocytes required to produce clinically overt pneumonia. The shared pulmonary pathological effects of CMV, irradiation, and cytotoxic drugs act additively or perhaps even synergistically; the effects of each factor in isolation produce only subclinical pneumonia, but acting together they may induce clinically apparent pneumonia.

Resolution of CMV pneumonia probably depends on the development of systemic and local virus-specific cytotoxic cell responses, though the magnitude of these pulmonary responses has not yet been shown to correlate with the likelihood of recovery. Withdrawal of iatrogenic immunosuppression facilitates resolution of the pneumonia by allowing cytotoxic cell responses to develop. The failure of antiviral chemotherapy to ameliorate CMV pneumonia in bone marrow allograft recipients reflects late treatment of the disease at a stage when irreversible lung damage has already occurred. Eradication of virus from the lung at this stage achieves little benefit. Pre-existing lung
damage induced by irradiation or cytotoxic drugs means that irreversible lung damage occurs earlier in the evolution of CMV pneumonia.

Role of Immunopathology

Grundy et al. propose that CMV pneumonia develops as a consequence of immunopathological damage to the lung parenchyma (5). This damage is supposedly mediated by T-cell reactivity directed against cells expressing viral antigens. Evidence cited in support of this hypothesis comprises the putative efficacy of CMV immune globulin in the treatment of CMV pneumonia, and the apparently immunopathological basis of pneumonia produced by murine cytomegalovirus (MCMV) in mice. Grundy and co-workers postulate that specific immune therapy promotes resolution of CMV pneumonia in man because antibody binds to viral or other antigens expressed on cells in the lung, thus blocking T-cell-mediated immune damage. There is however, no evidence to support this mechanism of action. Indeed, the therapeutic efficacy of immune globulin alone or in combination with ganciclovir remains unproven in CMV pneumonia (26,27).

The hypothesis that MCMV pneumonia is a T-cell-dependent immunopathological condition rests on the ability of GVHD to promote its development, the prophylactic efficacy of continuous therapy with the immunosuppressive drug cyclophosphamide, and the absence of the pneumonia in infected T-cell-deficient athymic nude mice (5). Also, the titre of virus in the lungs correlates poorly with the development of pneumonia, and inhibition of intra-pulmonary virus replication by ganciclovir does not prevent pneumonia (5). Nonetheless, a role for T-cell-mediated immunopathology in the pathogenesis of MCMV pneumonia cannot be taken of itself to imply a similar pathogenesis for CMV pneumonia in man. The two diseases are caused by different viruses invading different hosts, and at least some of the apparently immunopathological characteristics of MCMV pneumonia are not found in human CMV pneumonia. Continuous therapy with the immunosuppressive drugs cyclosporin and prednisolone does not prevent CMV pneumonia in renal, heart, or heart–lung transplant recipients (2,28), and high-dose methylprednisolone therapy is not effective when given with ganciclovir to bone marrow allograft recipients with this disease (4). CMV pneumonia occurs in patients given T-cell-depleted bone marrow allografts (29). The apparent absence of reports of severe CMV pneumonia in T-cell-deficient infants with DiGeorge syndrome (30) may reflect the extreme rarity of this syndrome rather than an involvement of T-cell-dependent immunopathological events in the pathogenesis of CMV pneumonia. The association between CMV pneumonia and acute GVHD in marrow graft patients can be explained by depression of cytotoxic cell responses following prednisolone therapy given for GVHD (see above) rather than by promotion of immunopathological events.

Implications

Interaction between pre-existing lung damage and the degree of immunosuppression in the pathogenesis of CMV pneumonia may explain the greater incidence of this disease in recipients of heart–lung rather than heart allografts, and its rarity in patients with AIDS. Transplant patients given heart–lung rather than heart grafts receive more intensive immunosuppressive therapy and develop more lung damage because of pulmonary allograft rejection (2), and patients with AIDS are unlikely to have pre-existing lung damage at least in the early stages of the disease. Thus an immunopathological pathogenesis for CMV pneumonia is not essential to explain the apparent rarity of CMV pneumonia in patients with AIDS (3). If previous lung damage promotes the development of CMV pneumonia, one might predict an increasing risk of CMV pneumonia in patients with AIDS later in the disease after multiple episodes of Pneumocystis carinii or other pneumonias.

The proposed pathogenesis for CMV pneumonia suggests two possible strategies by which this pneumonia might be prevented and its mortality reduced: first, by minimizing iatrogenic immunosuppression, and second, by avoiding factors which promote lung damage. The effectiveness of the first strategy is indicated by the rarity of the disease in cyclosporin-treated renal allograft recipients given no or only minimal doses of maintenance prednisolone (8). Its low incidence in bone marrow allograft recipients conditioned with low dose rates of TBI possibly indicates the effectiveness of avoiding pulmonary toxins (31). However, use of cyclosporin, an agent associated with a low incidence of GVHD (31), may also be important if excessive iatrogenic immunosuppressive is thereby avoided. As death from CMV pneumonia is a major determinant of the outcome of allogeneic marrow grafting (17), application of the above preventative strategies could be vital in improving the success of this transplantation procedure.

Currently, the most promising strategy for the control of CMV pneumonia in bone marrow transplant recipients is early administration of chemophylaxis to patients with pulmonary infection detectable in bronchoalveolar lavage fluid (32). In a
recently reported placebo-controlled trial, ganciclovir significantly reduced the incidence of subsequent CMV pneumonia in such patients. The haematological toxicity of ganciclovir (4) nonetheless probably precludes its similar use in renal transplant patients who have only a low incidence of CMV pneumonia (8).

The hypothesis that pre-existing lung damage hastens the onset of irreversible lung damage in patients with CMV pneumonia predicts that antiviral chemotherapy is more likely to be successful if it is given early in the disease or if pre-existing lung damage is absent. There is some evidence which supports this prediction (4). However, successful treatment of CMV pneumonia may only be possible when less toxic anticytomegalovirus agents become available.

References

