Cytomegalovirus (CMV) pneumonitis in AIDS patients: the result of intensive CMV replication?

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ABSTRACT: We report a case of fatal pulmonary disease in a patient infected with human immunodeficiency virus (HIV), where cytomegalovirus (CMV) was the only causative agent identified in the lungs at autopsy. The most prominent histopathological features were numerous interalveolar cells containing CMV inclusion bodies combined with scanty signs of inflammation.

We propose that the lung damage caused by CMV in acquired immune deficiency syndrome (AIDS) patients is a direct consequence of cytopathogenic effects of the virus related to the extent of active virus replication. Eur Respir J., 1992, 5, 362-364.

Cytomegalovirus (CMV) is a major opportunistic pathogen in patients with acquired immune deficiency syndrome (AIDS) [1]. The importance of CMV as a cause of pulmonary disease in AIDS is controversial. CMV is frequently isolated from bronchoalveolar lavage (BAL) fluid in patients infected with human immunodeficiency virus (HIV), and CMV inclusion bodies are also, if somewhat less often, detected in lung tissue at autopsy of AIDS patients [2-6]. The clinical relevance of these findings is, however, often unclear, because CMV is frequently associated with other pathogens in the lungs [2-6]. In most reports of patients with AIDS and pneumonitis, the presence of CMV in BAL fluid apparently did not influence the clinical outcome [7].

In the present paper, a case of fatal pulmonary disease in an HIV infected patient is described, where CMV was the only causative agent identified at autopsy.

Case report

The patient was a 36 yr old homosexual man with documented HIV infection since 1986. For several years he had suffered from episodes of bronchitis. Because of multidermal Varicella zoster virus infection, treatment with zidovudine was started in September 1988.

In December 1989, the patient was admitted to hospital because of dyspnoea on exertion during the preceding two weeks. Chest X-ray examination revealed a sparse, localized infiltrate at the base of the left lung. Haemophilus influenzae was isolated from the BAL fluid, and the isolate was susceptible to all antibiotics used later. BAL virus culture was also positive for CMV, but intranuclear inclusions were not detected on cytological examination. Because of suspected bacterial pneumonia, treatment was started with amoxycillin, and the patient was discharged after three days. The clinical manifestations persisted, and two weeks later the therapy was changed to ciprofloxacin. However, the patient's condition did not improve, and he was readmitted to the hospital in February 1990 with fever (39.5°C), dyspnoea and productive cough. Radiographic examination of the chest showed bilateral, diffuse, interstitial pulmonary infiltrates. BAL fluid cultures for bacteria, mycobacteria and fungi, and staining for Pneumocystis carinii and acid-fast bacteria were all negative. CMV was cultured from BAL fluid and throat washings, but no intranuclear inclusions were detected.

The white blood cell count was 2.3x10⁹·l⁻¹. The CD4+ T-cell number was 490x10⁹·l⁻¹ in October 1989, 50x10⁹·l⁻¹ in January 1990 and 16x10⁹·l⁻¹ in February 1990.

Bacterial pneumonia with chest X-rays showing diffuse bilateral infiltrates may be seen in HIV infected patients [8], and after bronchoscopic examination intravenous administration of cefuroxime (1.5 g t.i.d.) was therefore initiated, but the patient's condition continued to deteriorate. Ophthalmological examination two weeks after admission showed retinal haemorrhages and white exudates suggestive of CMV retinitis, and foscarnet (65 mg·kg⁻¹ t.i.d.) was given. Two days later a severe respiratory distress developed. Arterial blood gas examination performed while the patient breathed room air showed pH 7.27, oxygen tension 5.0 kPa with
Lung and autopsy specimens were cultured in human embryo cells in disease parts. CMV, while no other pathogenic microbes were isolated. Microscopy disclosed CMV-infected cells (black straight arrows). CMV: cytomegalovirus.

Fig. 1. - Lung tissue with thickened alveolar septa containing proliferating pneumocytes (black curved arrows) and numerous CMV-infected cells (black straight arrows). CMV: cytomegalovirus. (Haematoxylin and eosin; bar equals 10 \( \mu \)m).

Adrenals were slightly enlarged with haemorrhages and necrotic areas. Microscopy disclosed CMV-infected cells in diseased parts.

Lung and spleen autopsy cultures were positive for CMV, while no other pathogenic microbes were isolated.

The ultimate cause of death was assumed to be CMV pneumonitis.

**Methods**

BAL fluid, throat washings, urine, peripheral blood and autopsy specimens were cultured in human embryo fibroblast cells and observed for typical cytopathic effects diagnostic for CMV.

**Discussion**

It has been claimed that CMV in the lungs of AIDS patients is a passive bystander, and not a pathogen [5]. Nevertheless, it is evident that CMV may also cause severe symptomatic pulmonary disease in HIV-infected patients, as shown in this and other reports [3, 4, 7, 9].

The diagnosis of CMV pneumonitis was, in our opinion, well-documented in this patient, who died of respiratory failure. There was histological evidence of florid CMV infection in the lungs, CMV was cultured from lung specimens, and no other pathogen was found in lung tissue. Although remnants of previous probable bacterial pneumonia were detected at autopsy, there was no sign of ongoing bacterial pneumonia.

The CMV inclusion bodies were most often seen in alveolar luminal cells probably representing desquamated alveolar lining epithelium. It is possible that some of these virus-infected cells represent macrophages and/or fibroblasts, but this is difficult to ascertain from light microscopy. Others [10] have found, using in situ hybridization with CMV probes, that the virus infects pneumocytes, interstitial cells and occasional bronchial epithelial cells. However, in our case alveolar epithelial cells seemed the primary cell type to be infected.

There are only a few documented reports of CMV as the sole causative agent of symptomatic pulmonary disease in AIDS patients [3, 4, 6, 9]. This is in marked contrast to the high frequency of serious CMV pneumonitis in recipients of solid organs and allogeneic bone marrow allografts [11].

In transplant recipients with CMV pneumonitis, histological examination usually shows necrotizing inflammation with relatively few CMV-infected cells [12]. In the present case, however, the most prominent histopathological features were numerous cells in the alveoli containing CMV inclusion bodies combined with scanty signs of inflammation.

Different histopathological pictures have been reported in association with pulmonary CMV infection in AIDS patients [4, 6, 7]. The usual presence of concomitant pulmonary infections or neoplastic disease has made it difficult to assess whether the histological changes in these cases were due specifically to CMV. However, the strong correlation between high density of CMV inclusion bodies and severe, symptomatic pneumonitis, as seen in our patient, has been reported by others, regardless of coexisting pulmonary disease [4, 6].

The difference in histopathological features between AIDS patients and transplant recipients may well reflect different pathogenetic mechanisms. It has been suggested that CMV pneumonitis in allogeneic transplant recipients is caused by immune mechanisms mediated by a T-cell response to virally induced antigens expressed in the lungs, and severe necrotizing pneumonitis may occur in spite of suppression of virus replication during ganciclovir therapy [13, 14]. AIDS
patients with profound immune deficiency may be unable to mount the immune response necessary to cause CMV pneumonitis by this mechanism. In AIDS patients the lung damage may be due directly to cytopathogenic effects of CMV, related to the extent of active virus replication. Animal studies support this hypothesis described for CMV pathogenesis in AIDS patients [13], which is assumed to be a late event in a stage of profound immune deficiency, as demonstrated in the present case.

References