NONSPECIFIC RADIOGRAPHIC MANIFESTATIONS OF CYTOMEGALOVIRUS INFECTION IN 4 HIV-POSITIVE ADULTS – DIAGNOSIS THROUGH TRANS-BRONCHIAL BIOPSY

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We report on 4 HIV-positive adult patients who presented (over a 2-year period) with clinically significant cytomegalovirus (CMV) pneumonia requiring transbronchial biopsy for diagnosis. The patients were not on antiretroviral therapy. Clinical findings were nonspecific, sputum samples were negative, blood test results were non-contributory, and empirical treatment had failed. Radiological findings were extensive but nonspecific. Three of the 4 patients were co-infected with *Pneumocystis jirovecii* (PJP) pneumonia, further confounding the radiological diagnosis.

CASE 1

A 45-year-old man with a history of previous tuberculosis (TB) infection presented with a cough and chest pain. Sputum results and blood cultures were negative. The chest radiograph (CXR) demonstrated bilateral multifocal areas of patchy airspace disease, as well as a dominant focal area of density in the right upper lobe (Fig. 1). No effusions were noted. A presumed diagnosis of PJP was made, but the patient did not respond to treatment. Bronchoscopic biopsy confirmed CMV infection.

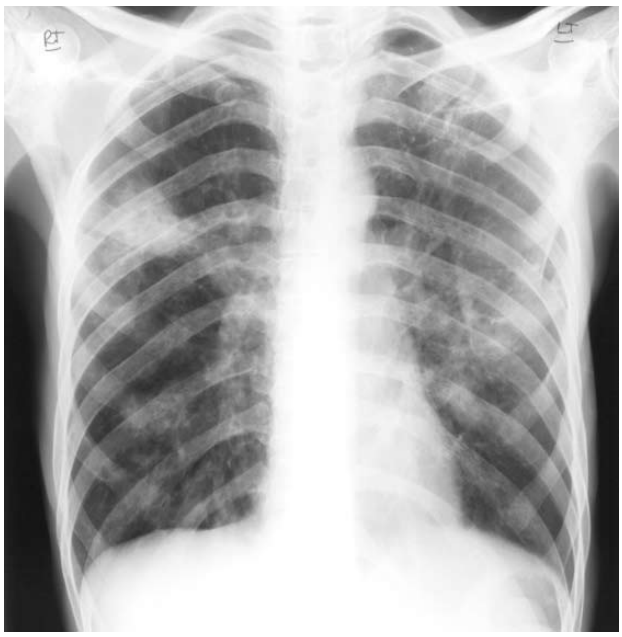


Fig. 1. The chest radiograph in patient 1 demonstrates bilateral multifocal areas of patchy airspace disease, as well as a dominant focal area of density in the right upper lobe.

CASE 2

A 43-year-old woman with no history of TB or TB contacts presented with a cough and haemoptysis, loss of weight, low fever and rigors. The white cell count (WCC) was 6.4×10^9/l, and sputum results and blood cultures were negative. The CXR revealed bilateral reticular-nodular and ground-glass opacities without any effusions (Fig. 2, a). The differential diagnosis included TB and PJP. Bronchoscopic biopsy confirmed the diagnosis of both CMV and PJP infections.

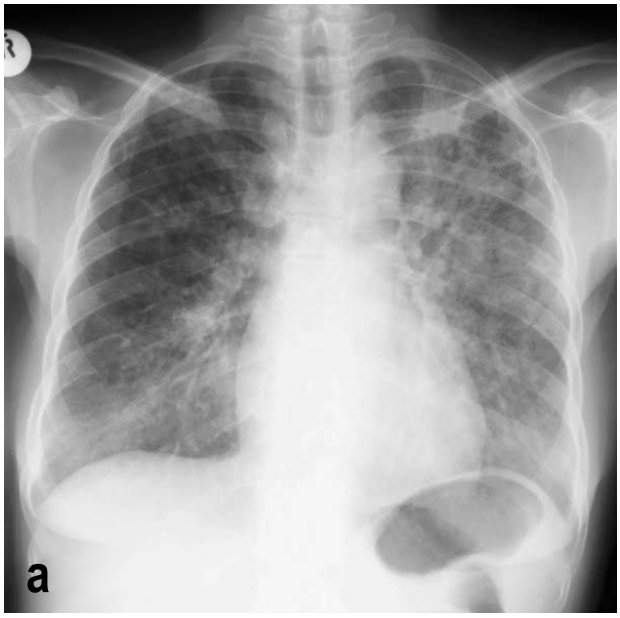
CASE 3

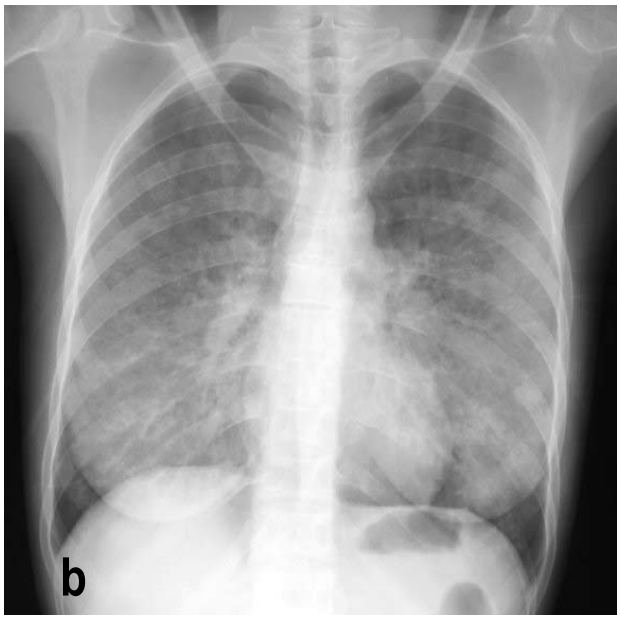
A 30-year-old woman presented with shortness of breath, a dry cough, loss of weight and fever. The WCC was 13×10^9/l and the CD4 count 481 cells/µl. The CXR demonstrated bilateral reticular and ground-glass opacities (Fig. 2, b). Treatment for TB and PJP was started, but the patient showed no clinical improvement. Bronchoscopic biopsy confirmed both CMV and pneumocystis pneumonia (PCP).

CASE 4

A 29-year-old woman presented with a cough, chest pain, loss of weight and shortness of breath. The WCC was 9.1×10^9/l and the CD4 count 14 cells/µl. On the CXR there were bilateral, diffuse, reticular and airspace shadows with no effusions (Fig. 2, c). Both TB and PJP were considered in the differential diagnosis. Transbronchial biopsy revealed CMV and PJP infections.

Transbronchial biopsy in all patients demonstrated alveolar tissue containing CMV with nuclear and cytoplasmic inclusions (Fig. 3). This was accompanied by alveolitis and an associated inflammatory cell infiltrate





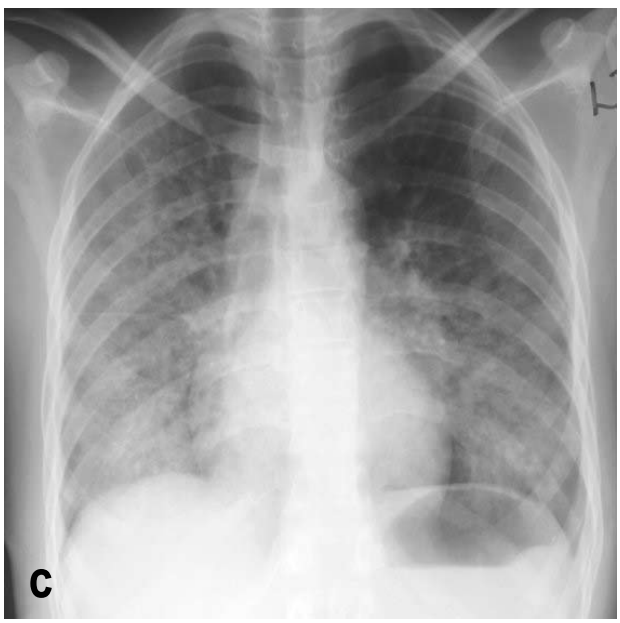


Fig. 2, a - c. In the chest radiographs of patients 2, 3 and 4, nonspecific bilateral reticular-nodular and ground-glass opacities were present with no features of an effusion.

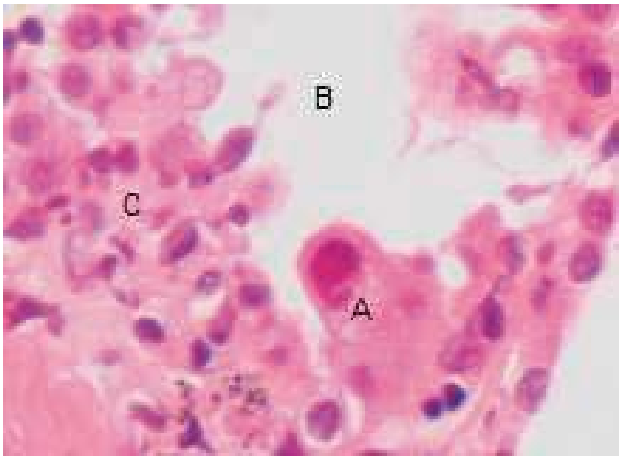


Fig. 3. Haematoxylin and eosin, high power. A = enlarged alveolar pneumocyte with brick-red intranuclear CMV inclusion body; B = alveolar space; C = alveolar wall showing a nonspecific inflammatory cell infiltrate. (Acknowledgement: Jill Murray, School of Public Health, University of the Witwatersrand and National Health Laboratory Service.)

of the alveolar walls. Ziehl-Neelsen staining and culture for TB were negative in all patients.

DISCUSSION

CMV is a relatively commonly identified pathogen in immunocompromised patients. This was first recognised in patients on immunosuppressive therapy for haematological malignancies or bone marrow and other organ transplants. In the South African setting, most CMV infections occur in patients with HIV/AIDS. CMV disease usually occurs in patients with low CD4 counts (<100 cells/μl).[1] Disseminated infection is relatively common and may manifest clinically as retinitis, encephalitis, hepatitis, oesophagitis or colitis. Clinically significant pulmonary infection is uncommon. However, CMV may be isolated in more than half of broncho-alveolar lavage (BAL) specimens in AIDS patients with pulmonary symptoms.[2]

In most patients, CMV infection co-exists with other opportunistic infections, particularly PCP. In this setting, there is doubt regarding to what extent CMV is acting as a pathogen.[3] The diagnosis of CMV pneumonitis is therefore often based on typical symptoms of fever, shortness of breath, hypoxaemia and diffuse infiltrates on the CXR in combination with detection of the virus in BAL fluid and the absence of other pathogens.[4] However, because of the high rates of co-infection, a definitive diagnosis of CMV requires identification of CMV intranuclear or cytoplasmic inclusion bodies in transbronchial biopsy specimens (used in our patients) or open lung biopsy specimens.[5]

Routinely securing a tissue diagnosis in the local setting is impractical and may be dangerous in patients with certain conditions, e.g. thrombocytopenia.[4] In one study examining AIDS patients undergoing diagnostic bronchoscopy for pulmonary symptoms, 72% had CMV cultured from BAL fluid but only 2 had pathological

evidence of CMV pneumonitis. Only 1 of these patients had autopsy confirmation that the cause of death was CMV pneumonitis.[6] In practice, treatment is therefore usually aimed at all other organisms, and only if the patient does not improve is anti-CMV therapy initiated.

In patients with pathologically proven CMV pneumonia, CXRs usually show bilateral, reticular, interstitial disease that classically begins in the periphery of the lower lobes and spreads centrally and superiorly, as seen in 3 of our patients. Focal infiltrates, nodules and diffuse alveolar infiltrates are less common findings and were noted in 2 of our patients.[7] Because of the nonspecific clinical presentation, clinicians tend to rely on imaging to distinguish between CMV and PJP. However, it is usually impossible to differentiate between these two conditions on the basis of radiographic findings. In this context some consider thin-section computed tomography (CT) to be the investigation of choice.[1] CT scans may reveal bilateral or focal ground-glass or consolidative changes, as well as (less commonly) well-defined solitary or multiple nodules measuring up to 3 cm in diameter,[8] which makes CT also poor at differentiating between PCP and CMV infection. In a study comparing CT findings in these two infections in 58 immunocompromised HIV-negative patients, small and centrilobular nodules, unsharp demarcation of the ground-glass infiltrates and consolidation favoured CMV pneumonia, while an apical distribution and the occurrence of a mosaic pattern suggested PCP.[1] Although CMV usually mimics PCP, the radiological differential diagnosis of diffuse interstitial pulmonary infiltrates in AIDS also includes infections with other organisms.

CONCLUSION

Even though CMV is a relatively commonly identified organism in BAL specimens from immunocompromised HIV patients, CMV pneumonia is uncommon. As demonstrated in our patients, CMV pneumonitis typically has a nonspecific plain radiographic presentation which overlaps with that of PCP, a common co-infection. The diagnosis then relies on transbronchial biopsy. In sub-Saharan Africa, where a large proportion of patients are not yet on antiretroviral therapy and have low CD4 counts, CMV remains an important differential diagnosis in pneumonia in HIV/AIDS. Where there are resource limitations for performing bronchoscopic biopsy, failure of a trial of therapy and diffuse interstitial or patchy airspace disease on CXR should prompt the clinician to initiate treatment for CMV.

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