Cytomegalovirus Pneumonia in Adult Acute Lymphoblastic Leukemia


Abstract
Cytomegalovirus (CMV) is an important cause of morbidity and mortality in immunosuppressed patients. Though acute lymphoblastic leukemia (ALL) is an immunosuppressed state, CMV disease has been reported infrequently. We present a patient of adult B lineage ALL who was on maintenance chemotherapy and developed CMV pneumonia. Patient was managed with intravenous ganciclovir and had successful outcome. However, three weeks later patient had a relapse of ALL and died shortly after high dose chemotherapy.

INTRODUCTION
Cytomegalovirus (CMV) is an important cause of morbidity and mortality in immunosuppressed patients especially patients who have cell mediated immunodeficiency either because of the disease (e.g. acquired immune deficiency syndrome because of HIV) or because of treatment (e.g. post transplant, treatment with purine analogues). Though the incidence of CMV disease is increasing all over the world, it is reported infrequently in patient with B lineage acute lymphoblastic leukemia (ALL). We report an adult patient of B lineage ALL who was on maintenance phase of chemotherapy and developed CMV pneumonia.

CASE REPORT
An 18-year-old male was seen in the out patient follow-up clinic with complaints of progressive shortness of breath and dry cough of 15 days duration. He was earlier diagnosed as a case of Pre-B-cell ALL and was on treatment with modified BFM protocol. His last bone marrow examination done 3 months back showed him to be in remission and he was on maintenance phase of chemotherapy with daily 6-mercaptopurine, weekly methotrexate and monthly pulses of vincristine and prednisolone and intrathecal methotrexate three monthly. Patient did not receive prophylaxis for Pneumocystis jiroveci in the form of Co-trimoxazole. He did not have any major episodes of febrile neutropenia during chemotherapy. He was treated with oral levofloxacin on out-patient basis without significant response.

Physical examination revealed a thin male who was afebrile but tachypnoeic (respiratory rate 36/minute) and cyanosed. His blood pressure and central venous pressure (CVP) were within normal range. His respiratory system was otherwise unremarkable except for high respiratory rate. Other systems were within normal limits. Investigations revealed hypoxemia on room air (oxygen saturation of 60%, PaO₂-38 mm Hg), leukopenia with a total count of 1.0 x 10⁹/L, absolute neutrophil count and an absolute lymphocyte count of .48 x 10⁹/L each. Hemoglobin was 15.4gm/dl and platelet count was 430 x 10⁹/L. Liver and renal function tests were normal. Two blood cultures were sterile. Chest x-ray revealed bilateral, asymmetric, lower lobe predominant, interstitial and alveolar opacities. High resolution CT scan (HRCT) of the chest revealed diffuse interstitial thickening with ground glassing involving predominantly lower lobes of both lungs. Sputum microscopy was negative for bacteria, fungus (including Pneumocystis jiroveci) and cultures were sterile.

Based on this picture, maintenance chemotherapy was withheld and patient was started an empiric antibiotics consisting of cefpime and teicoplanin, along with co-trimoxazole to cover pneumocystis infection. On the third day of admission, because of non-response to antibiotics, empiric amphotericin B deoxycholate in the dose of 1mg/kg/day was added.

However, patient condition did not improve and infiltrates on the subsequent chest X-ray increased. Mechanical ventilation had to be instituted when his...
respiratory failure could no longer be managed by non-invasive means. On day+14 of his hospital admission, his blood samples tested positive for CMV pp65 antigen by indirect immunofluorescence. His qualitative blood PCR sent on the same day for CMV-DNA was also positive. The hematological parameters of the patient at this time were hemoglobin 14.5 gm/dl, WBC 7.2 x 10^9/l and platelets 231 x 10^9/L.

Patient was started on therapy with Ganciclovir, in a dose of 10mg/kg/day in two divided doses. Fibre-optic bronchoscopy with broncho-alveolar lavage (BAL) was done on the fifth day of mechanical ventilation. BAL fluid PCR for CMV DNA and staining for inclusion bodies were however negative. Lung biopsy was deferred due to inherent risks of the procedure in mechanically ventilated patients. BAL fluid for PC jeroveci by methenamine silver stain was negative. Co-trimoxazole was stopped based on non-response and negative BAL fluid report. The patient showed a remarkable response to ganciclovir therapy; chest x-ray showed clearance of infiltrates partially, blood gases improved, ventilatory requirements diminished and he could be weaned off in 12 days. Therapy with ganciclovir was continued for a period of 21 days and he was discharged from hospital. His CMV antigen at discharge was negative. Three weeks later, patient presented with decrease in vision. Fundus was unremarkable but cerebrospinal fluid examination was positive for malignant cells. Bone marrow examination did not reveal increase in blast cells. He was diagnosed as isolated meningeal relapse and was treated with high-dose methotrexate and cytarabine; however, he succumbed to septicemia following chemotherapy.

**DISCUSSION**

CMV is an important pathogen in immunosuppressed patients, including those with lymphoproliferative disorders, in whom it causes a variety of clinical syndromes.1,2 Even in immuno-suppressed patients, it has been reported more frequently in T cell ALL/Lymphoma than B cell disease.4 Our patient developed disease with the virus at a fairly late stage of his treatment, i.e. in the maintenance phase, wherein the degree of immunosuppression was actually less intensive than in the preceding induction, consolidation and reinduction phases. An earlier study in adults with ALL has noted a mean duration of nine months between the diagnosis of leukemia and the CMV disease.1 It has also known that CMV viral load can go up in immunosuppressed patients who had been previously infected with CMV, however, this does not indicate active infection. Definite CMV disease can only be diagnosed in presence of organ dysfunction and showing presence of CMV from that particular organ either by cultures, histopathology, immuno-histochemistry or molecular techniques.1,2

Definite CMV pneumonia has been defined in various studies as the presence of a classical clinico-radiological picture suggestive of the condition with either histological evidence of viral infection, or virological evidence in the form of positive viral culture from biopsy specimens or BAL fluid.3 PCR of BAL fluid for CMV DNA has not been sufficiently standardized for its consistent use in CMV pneumonia; even though some studies have used it as a diagnostic modality.3 Bilateral, yet asymmetric, lower lobe predominant, interstitial infiltrates with ground-glassing, with occasional nodules are the most frequent findings on HRCT.4 In the present case, we did not demonstrate CMV either in BAL specimen or lung tissue. However, BAL examination was done 5 days after start of ganciclovir therapy and that may be one of the reasons for it to be negative. Typical clinico-radiological picture with excellent response to ganciclovir in the present case would label the present case as probable CMV pneumonia and not definite CMV pneumonia.5 Previous studies have shown a dismal prognosis in patients who have required mechanical ventilation, inspite of ganciclovir, especially those in whom it was initiated within twenty-four hours or after the institution of ventilation. Concurrent pulmonary infections with other organisms, fungi (Aspergillus sp., Pneumocystis jeroveci), viruses (Respiratory syncytial virus, Parainfluenza, Adenovirus) and bacteria (including Mycobacteria) have been observed in 30-40% of cases. In this subset of patients the prognosis is markedly worse.1,2 In our patient, no concurrent infection could be demonstrated. Another interesting aspect of the case is that the leukemia relapsed within few days of completion of treatment for CMV pneumonia. Whether impending relapse predisposes the patient to more immunosuppression and infection is an interesting hypothesis that is difficult to prove.7

**REFERENCES**