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Keywords
Cytomegalovirus; β-thalassemia; splenectomy; blood transfusion; pneumonitis

Running Head
CMV pneumonitis in a splenectomized patient
Summary: Cytomegalovirus (CMV) rarely causes disease in immunocompetent individuals but may cause severe disease in immunocompromised patients. We report the case of a multi-transfused, splenectomized young woman due to homozygous β-thalassemia that presented with prolonged fever and respiratory distress. Although broad-spectrum antibiotic therapy had initially been applied, the patient was clinically deteriorated. Serology and molecular blood testing established CMV infection and viremia. Computed tomography of the chest demonstrated pneumonitis and she was successfully treated with 3 weeks ganciclovir. In splenectomised β-thalassemic patients necessitating multiple blood transfusions, CMV-infection should be considered in the differential diagnosis.

Text

β-thalassemia major is a hereditary disorder characterized by genetic deficiency in the synthesis of beta-globulin chains that may lead to transfusion-dependent anemia. Splenectomy is usually performed to reduce excessive blood consumption and consequent severe iron overload. Although a patient with thalassemia major should not be considered as immuno-compromised per se, infection is a common cause of death in thalassemia major patients. Cytomegalovirus (CMV) is a member of the Herpesviridae family that is transmitted between humans through sexual intercourse, placenta, breast-feeding, saliva, blood transfusion and transplantation of solid organs or hematopoietic stem cells (1). In healthy individuals, primary CMV infection is presented as an asymptomatic or self-limiting mononucleosis-like febrile illness. However, severe life-threatening disease has been described in immunocompromised patients (2).

A 36-year-old woman was generally well until one week before admission to another hospital, when she developed fever with a temperature up to 38°C, chills and fatigue. A chest radiograph, urine and blood cultures were reported negative at that time. The patient was commenced on amoxicillin-clavulanate, without any clinical improvement and she was then transferred to the University Hospital of Heraklion 5 days later for further evaluation. The patient
had a history of homozygous β-thalassemia necessitating transfusions with packed red blood cells every ten days, asplenia due to splenectomy, secondary liver hemosiderosis along with hepatomegaly, secondary thrombocytosis and hypothyroidism. Her medications included deferiprone, levothyroxine and folic acid. Pneumococcal and meningococcal vaccinations had been administered before splenectomy. No allergies, smoking, alcohol drinking or use of illicit drugs were reported.

Upon admission, her temperature was 38°C, blood pressure was 110/60mmHg, pulses were 100 beats per minute, respiratory rate was 20 breaths per minute and the oxygen saturation was 88% while she was breathing ambient air. Physical examination revealed decreased breath sounds with crackles at the bases of the lungs, palpable axillary lymph nodes and tender hepatomegaly. The rest of the clinical examination was unremarkable. Chest radiograph revealed diffuse consolidation in both pulmonary bases with co-existing pleural effusions (Fig. 1). Arterial blood gas values were pH=7.425; PaCO₂=43.5mmHg; PaO₂=51.8mmHg; and HCO₃=29.9mmol/L while the patient breathed room air. The white-cell count was 25,700/mm³, with 36.9% polymorphonuclear cells, 53% lymphocytes, 6.9% monocytes, and 3% eosinophils. The hemoglobin level was 11.5g/dL, and the platelet count was 981,000/mm³. The aspartate aminotransferase level was 34U/L (normal range, 8 to 40), and the alanine aminotransferase level was 55U/L (normal range, 8 to 40), gamma-glutamyl-transferase was 117U/L (normal range, 8 to 40). The erythrocyte sedimentation rate was 53mm/hour, and the C-reactive protein level was 4.2 mg/dl (normal range, 0.08 to 0.8). The patient had been commenced initially on ceftriaxone intravenously, however, due to rapid clinical deterioration with high fever (temperature up to 40°C) and dyspnea the antimicrobial therapy was changed to meropenem (1gr tid), moxifloxacin (400mg od) and vancomycin (1gr bid). A high resolution computed tomography of the chest was performed demonstrating diffuse consolidation and atelectasis of both lower pulmonary fields and pleural effusions, as well as a micro-nodular interstitial pattern of both lungs (Fig. 2). Blood and urine cultures were sterile. A transthoracic echocardiography was normal with no valvular vegetations. Tests for antibodies against human
immunodeficiency, hepatitis B and C, and CMV viruses upon admission, as well as urine antigens for *Legionella pneumophila* and *Streptococcus pneumoniae* were negative. Subsequent serological tests for CMV (ARCHITECT CMV IgM assay (chemiluminescent microparticle immunoassay (CMIA) ABBOTT) and enzyme-linked immunosorbent assays (ELISA) for the detection of IgG and IgM antibodies to CMV in human serum (SERION ELISA classic CMV IgG and IgM tests)) showed increased levels of IgM antibodies (0.91AU/mL, positive > 0.8AU/mL) and low IgG antibodies (2AU/mL, negative < 15AU/mL) which were increased after 5 days (IgM 3.16AU/mL and IgG 15AU/mL), consistent with acute CMV infection. Quantitative polymerase chain reaction (qPCR) for CMV (artus® CMV QS-RGQ Kit - Qiagen) was also positive (10^5 copies/mL) in plasma. Bronchoscopy was normal and the bronchoalveolar lavage showed lymphocytosis with a CD4 to CD8 ratio of 0.3. The patient was commenced on ganciclovir (5mg/kg/12h) and became afebrile on day 5 of ganciclovir treatment. She received intravenously ganciclovir for two weeks and was continued on oral valganciclovir 900mg per day at home for one more week. One month later she was in good condition without any evidence of infection.

Severe CMV infections have been described in splenectomized patients after major surgery or severe trauma (3–5). Five cases of severe pneumonitis have been reported in patients with post-traumatic splenectomy and multiple transfusions (5). All of them had a long period of high fever, severe interstitial pneumonitis with hypoxemia and marked lymphocytosis with numeral atypical lymphocytes as in our case. While writing this case report, another group published a similar case (6) by making these the first two cases of CMV pneumonitis in patients with β-thalassemia major and splenectomy.

It is widely known that splenectomy reduces humoral response and is a risk factor for invasive infection by encapsulated bacteria. However, changes of cellular immunity have been reported after splenectomy such as decreased natural killer activity and weakened IgM memory B cell response (7-8). Therefore, impaired immune response may be associated with increased severity and uncommon manifestations of CMV infection in splenectomized patients.
Furthermore, individuals with splenectomy and thalassemia should be considered as at high risk for CMV infection due to high prevalence of transfusion-transmitted disease (9). During the last decades, serological testing and blood-component leukoreduction have been used to reduce the risk for CMV transmission in patients necessitating transfusions (2). Therefore, serological and molecular screening should be suggested in high risk patients.

CMV pneumonitis is a life-threatening disease in immunocompromised patients and is diagnosed by the detection of CMV in bronchoalveolar lavage fluid or lung tissue samples (10). In our case, increased lymphocyte differential count and low CD4 to CD8 ratio in the bronchoalveolar lavage as well as the micro-nodular interstitial pattern of lung in the context of CMV viremia and the rapid clinical response to ganciclovir supported the diagnosis of CMV pneumonitis.

In conclusion although CMV pneumonitis is an extremely rare clinical manifestation among immunocompetent patients, in splenectomized thalassemic patients with pneumonitis, CMV infection should be included in the differential diagnosis.

**Conflict of Interest**

None to declare.

**References**


Fig. 1. Chest X-ray revealed diffuse consolidation in both pulmonary bases with co-existing pleural effusions.

Fig. 2(a-b). High resolution computed tomography of the chest demonstrated diffuse consolidation and atelectasias of both lower pulmonary lobes and pleural effusions (Fig. 2a). Intrapulmonary, an
homogeneous air pattern was seen, especially in the right middle lobe. Multiple pulmonary micronodules were revealed in both upper lobes, the right middle lobe and both apical segments of the lower lobes (Fig. 2b). Enlarged lymph nodes were found in both lung hilums, as well as thickening of the anterior pericardium.