Hemoptysis in Patient with Febrile Neutropenia and Early T-Cell Precursor Acute Lymphoblastic Leukemia

Enrica Bertelli, 1 Concetta Micalizzi, 2 Elio Castagnola 1

Summary

A 16-year-old girl had been undergoing intensive chemotherapy (ALL 2009) for Early T-cell precursor acute lymphoblastic leukemia (ETP). At 22:00 of the 26th day of induction phase IA, she was found to have developed febrile neutropenia. After blood cultures were obtained, empirical therapy with ceftriaxone and amikacin was initiated, according to internal protocol. Clinical condition improved and she remained afebrile for 24 hours. The following day, at 04:00, she suddenly developed a cough with hemoptysis. At this time, fibrinogen was 167 mg/dL, and platelets 35000/uL. A chest X-ray showed thickening in the middle of the right lower zone, and a chest CT scan showed a nodule with central hypodense area (necrotic-colliquative evolution of the infiltrate). In spite of supplementation with platelets, red blood cells, plasma, fibrinogen, antithrombin, and activated factor VII, the patient's clinical condition worsened rapidly and the pulmonary hemorrhage became uncontrollable. She died at 12:00. Blood cultures yielded a strain of Pseudomonas aeruginosa, with reduced sensitivity to antibiotics.

Aspergillosis is the most frequent infectious cause of massive pulmonary hemorrhage in pediatric leukemias, while bacterial pneumonia or TBC are by far less frequent. Aspergillus requires the presence of neutrophils to cause hemoptysis or cavitation, while bacteria (Gram-positive or -negative) can cause pulmonary necrosis also in patients with neutropenia.

Case report

A 16-year-old girl, who had been diagnosed with Early T-cell Precursor acute lymphoblastic leukemia (ETP) one month earlier, had been undergoing chemotherapy based on the AIEOP-BFM (Italian Association of Pediatric Hematology Oncology-Berlin-Frankfurt-Münster) ALL (acute lymphoblastic leukemia) 2009 protocol [European Clinical Trials Database 2007-004270-43] for patients with HR (high risk) and prednisone good response (PGR); she had high minimal residual disease (a high-risk criterion), as on day 15, bone marrow blasts hd resulted at ≥10% 1 by flow cytometry (84%).
The patient was a smoker and used oral contraceptives. The patient developed fever at 22:00 of the 26th day of induction phase IA, after the second pegylated L-asparaginase (Oncaspar) infusion, while under treatment with dexamethasone. She had developed prolonged aplasia, and was platelet (PLT) and red blood cell (RBC) transfusion dependent at the time (WBC 100/μL, Hb 9.5 g/dL, PTL 35000/μL), with a clotting time of PT ratio 1.14 (n.v. 0.80-1.33), fibrinogen 167 mg/dL (n.v. 170-400), and antithrombin 81% (n.v. 70-120). CRP was 3.6 mg/dL (n.v. <0.46).

After blood cultures were obtained, the patient received empirical antibiotic therapy with ceftriaxone and amikacin, according to internal protocol. Clinical condition improved and she remained afebrile for 24 hours.

On day 28, at 04:00, she suddenly developed a cough with hemoptysis. A chest X-ray showed thickening in the middle of the right lower zone, and a chest CT scan confirmed the basal lesion with central hypodense area (necrotic-colliquative evolution of the infiltrate). In spite of supplementation with platelets, RBC, plasma, fibrinogen, antithrombin, and activated factor VII, the patient's clinical condition worsened rapidly and the pulmonary hemorrhage became uncontrollable. At 10:00, blood cultures yielded a strain of Pseudomonas aeruginosa, with reduced sensitivity to antibiotics. Treatment with Meropenem and Ciprofloxacin was immediately started. The patient died at 12:00.

Discussion
ETP leukemia is characterized by poor early response to conventional induction treatment. Full efficacy of treatment is achieved in consolidation phase IB. Although the number of patients and observation period are still limited, patients with ETP treated with the current AIEOP-BFM stratification and treatment strategy show a favorable outcome compared with earlier reports. The potential role of innovative treatments and haemopoietic stem cell therapy in ETP needs to be assessed.

The possible infectious causes of hemoptysis, a rare but severe complication of pediatric leukemia, include: invasive mycosis, such as Aspergillosis (which is the most frequent), bacterial pneumonia or tuberculosis.

A recent review of the literature showed that massive hemoptysis is an underestimated cause of death in patients with acute leukemia in remission and pulmonary filamentous mycosis. In patients with fungal infections, pneumonia may occur by two different mechanisms. During profound neutropenia, the pulmonary lesions may be caused by direct vascular damage by the fungus, possibly through the release of proteolytic enzymes by the Aspergillus itself. A second possible mechanism is the disruption of vascular structures by necrotizing acute inflammation factors (e.g. oxygen radicals) released by granulocytes. We believe that the second mechanism is prevalent in patients affected by pulmonary complications during or immediately following bone marrow recovery. The pathogenesis of pulmonary cavitation is probably related to both the tissue damage induced by the organism and the host reaction. Fungal lesions in neutropenic patients usually present with the typical halo sign (e.g., a macronodule, >=1 cm in diameter, surrounded by a perimeter of ground-glass opacity) or as nodular lesions, not with cavitary lesions that become apparent only after neutrophil recovery. In patients with pulmonary aspergillosis, a (too) rapid recovery of the granulocyte count may be associated with the development of severe complications, like pneumothorax or fatal hemoptysis.

The observation of a cavitary lesion in a febrile and neutropenic patient with acute leukemia should raise the suspicion of a bacterial infection rather than a mycosis due to filamentous fungi, especially in presence of positive blood cultures (e.g., Staphylococcus aureus or Gram-negative rods, mainly from the Klebsiella-Enterobacter-Serratia (KES) group or Pseudomonas), because bacteria themselves disrupt vascular structures.
Figure 1: Pulmonary cavitary lesions resulting from different etiologies, in the presence and absence of neutropenia. A. Neutropenic patient with hemoptysis and pulmonary cavitation in presence of Pseudomonas aeruginosa bacteremia (Case report). B. No-longer neutropenic patient with pulmonary aspergillosis with arterial perforation C. Air crescent in a no-longer neutropenic patient with pulmonary aspergillosis.
Tuberculosis due to *Mycobacterium tuberculosis*, although not common in cancer patients, may present as either localized pulmonary disease or devastating miliary infection in patients receiving antineoplastic chemotherapy or HSCT. Other laboratory biomarkers, such as galactomannan antigen and β-D-glucan are useful for early diagnosis. The current gold standard imaging technique is computed tomography (CT) scan to show the thoracic lesions. The evolution of the lesion toward aspecific nodules (the most frequently observed lesions in pediatrics) and a crescent of air in a cavity (if the patient is no longer neutropenic) are suggestive of pulmonary aspergillosis, but other filamentous fungi like *Zygomycetes* (now identified as *Glomeromycetes*) can also cause similar lesions, even though pulmonary zygomycosis is more frequently associated with the presence of multiple (>10) bilateral lesions and severe pleural effusion. Therefore, understanding the epidemiology of invasive fungal diseases within the affected healthcare facility is essential for evaluating the risk of non-*Aspergillus* mold infections. The choice of the empirical broad-spectrum treatment to use in neutropenic patients with a pulmonary infiltrate should be based on the type of infiltrate, the time of appearance of the infiltrate in relation to the onset of fever, and epidemiologic and anamnestic data. For example, *viridans streptococci* have been associated with acute respiratory distress syndrome in neutropenic patients with severe oral mucositis. If this is a likely possibility, penicillin in combination with a glycopeptide appears to be the most logical treatment choice. If pneumonia is evident from the beginning of the febrile episode, a bacterial etiology should be suspected, and the same antibiotic regimen commonly used for febrile neutropenia in high-risk patients should be used, taking into account the potential presence of highly resistant pathogens. To combat the leading cause of bacterial pneumonia in children (S. Pneumoniae, accounting for 28-33% of all cases in hospitalized patients), the 13-valent pneumococcal vaccination was strongly recommended in Italy for all newborns and at-risk children and adults with (including those with oncohematological pathologies). On the contrary, if pneumonia appears to occur as a breakthrough infection in a patient already receiving broad-spectrum antibiotics, fungal etiology is more likely and antifungal therapy is the logical step to take, although infection caused by a resistant bacterial pathogen, such as *Legionella* or *Mycoplasm pneumoniae*, is also possible. Interstitial pneumonia is relatively rare during neutropenia, but it does occur. In such cases CMV, influenza virus, *Pneumocistis jirovecii*, and *M. pneumo- niae* are the likely culprits. In conclusion, *Aspergillus* requires the presence of neutrophils to cause hemoptysis or cavitation, while bacteria (Gram-positive or -negative) can cause pulmonary necrosis also in patients with prolonged neutropenia.

**Conflict of Interest Disclosure:** All the authors declare that they have not received support from any company for the submitted work, nor do they have any kind of relationships with any company that might have an interest in the submitted work or have financial or non-financial interests that may be relevant to the submitted work. They also declare that their spouses, partners, or children have not had any relationship with financial implications that may be relevant to the submitted work.

**References**


