Pulseless Right Upper Limb: An Unusual Manifestation of Invasive Pulmonary Aspergillosis in Acute Myeloid Leukemia

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Abstract
Aspergillus is the most common cause of fungal pneumonia in acute leukemia patients receiving chemotherapy or undergoing hematopoietic stem cell transplantation. Despite a high index of suspicion and prompt institution of specific antifungal therapy, it causes significant morbidity and mortality in patients with hematological malignancies. It has to be differentiated from mucormycosis because the treatment differs. Histological confirmation obtained by lung biopsy is ideal, but is difficult to obtain in those patients who often have thrombocytopenia. We report a case of acute megakaryoblastic leukemia with typical manifestations of invasive pulmonary aspergillosis who developed pulseless right arm due to invasion of the right subclavian artery. When total leucocyte counts recovered, patient also developed immune reconstitution inflammatory syndrome and massive pulmonary hemorrhage, which was managed by bronchial artery embolization.

Introduction
Patients with haematological malignancies are at increased risk of fungal infections. Infections particularly by aspergillus and zygomycosis can progress rapidly and may be highly destructive to local tissues. Prompt diagnosis preferably with tissue biopsy and early institution of antifungal therapy with debridement of involved organ is required, but this approach is not usually feasible in patients with hematological malignancies who may have thrombocytopenia and disseminated intravascular coagulation. Further, microvascular invasion is a well known manifestation of invasive fungal infection in immunocompromised patients but large artery obstruction has rarely been reported. There are only a few sporadic case reports of subclavian artery obstruction by invasive pulmonary aspergillosis (IPA). Moreover, not only low neutrophil count is a risk factor for invasive aspergillosis but also rising neutrophil count can cause local tissue destruction by the phenomenon of immune reconstitution inflammatory syndrome (IRIS). Insipde of aggressive treatment the prognosis of invasive pulmonary aspergillosis is usually poor.

Case Report
A 25-years-old man, with acute megakaryoblastic leukemia, had received induction chemotherapy with daunorubicin (45mg/m² for 3 days) and cytarabine (100mg/m² continuous infusion for 7 days) and was in remission. During induction chemotherapy high resolution computed tomography (HRCT) of chest showed nodular opacities with surrounding ground glass haze suggesting fungal pneumonia and was treated with antifungal drug Voriconazole (200mg twice daily). These lesions subsequently resolved. He received one course of consolidation chemotherapy with high dose cytarabine (total 18g/m² over 5 days). He was on secondary antifungal prophylaxis with Voriconazole (200mg once daily). He tolerated his first consolidation chemotherapy well without flare-up of pneumonia.

On day 20 following second course of consolidation with cytarabine, the patient developed sudden onset high grade of fever, pain in the right chest and right arm, and dry cough. On examination he was found to have absent pulses in right upper limb, however, the limb remained warm with adequate nail-bed circulation. He was febrile with oral temperature of 103°F, pulse rate and blood pressure of 108/min and 110/68mmHg respectively, in left arm supine position. His haemoglobin was 7.9 g/dl, total leukocyte count of 11.0/µl (absolute neutrophil count 22/µl) and platelet count 20000/µl, prothrombin time (PT) 19/12seconds and activated partial thromboplastin time (aPTT) 39/30seconds. Chest radiograph showed right upper zone consolidation (Figure 1).

Emergency CT-angiogram showed encasement and occlusion of the right subclavian artery contiguous with the adjacent lung consolidation (Figure 2). Intravenous antibiotics (Cephaperazone plus sulbactum and Amikacin) and Granulocyte Colony Stimulating Factor (G-CSF, 300µg subcutaneously, daily) were administered. Considering progression of the disease on voriconazole, it was replaced with Amphotericin-B (1.5mg/kg) because the invasive nature of the lesion on imaging suggested the clinical possibility of mucormycosis. He could not be taken up for arterial recanalization procedure because of the persistently low platelet counts and coagulopathy despite regular single donor platelet and fresh frozen plasma transfusions.

The patient remained on conservative management. He did not develop any gangrenous changes in the affected limb presumably due to development of collateral circulation. Serial blood cultures remained negative for bacteria and fungi. On day 40 his platelet counts increased to 56000/µl and the coagulopathy improved (PT 13/12 secs and aPTT 32/30 secs). Ultrasound
guided percutaneous fine needle lung aspiration and trucut biopsy on day 41 revealed fungal hyphae branching at acute angle suggesting Aspergillus sp. (Figure 3). He became afebrile on day 44. His absolute neutrophil count increased to 1800/µl on day 46. Follow up chest radiograph (Figure 4a) on day 47 showed worsening of consolidation suggestive of immune reconstitution inflammatory syndrome (IRIS), though he remained clinically and hemodynamically stable. On day 49, the patient developed massive hemoptysis perhaps as a part of IRIS, since there was no bleeding from any other site. He was given blood, platelets and plasma support, his platelet count was 62000/µl and PT (13/12sec) and aPTT (32/30 secs) at that time were within normal limits. Urgent bronchial artery embolization (Figures 5a and 5b) was carried out. This immediately stopped further bleeding with simultaneous symptomatic improvement. Chest radiograph on day 54 showed radiological improvement in consolidation (Figure 4b). He remained clinically stable and afebrile until day 62 when he developed sudden onset breathlessness and hypotension presumably due to pulmonary embolism and could not be revived.

Discussion

Invasive pulmonary aspergillosis (IPA) was first described in 1953 by Rankin.2 The incidence of IPA has increased in the past two decades largely due to widespread use of chemotherapy and immunosuppressive agents.3 The angioinvasive nature of aspergillus is directly related to its ability to digest elastic tissue, a characteristic mediated by production of the enzyme elastase.4 During neutropenia, the classic clinical picture of invasive pulmonary aspergillosis is that of persistent or recurrent fever associated with signs of pulmonary infarction in the form of dry cough and pleuritic chest pain. Hemoptysis is more frequently reported after bone marrow recovery. Neutropenia, especially absolute neutrophil count <500/µl is the most important risk factor for development of IPA. It is strongly related to the duration and degree of neutropenia. Early diagnosis of IPA in severely immunocompromised patients is difficult, and a high index of suspicion is necessary in patients with risk factors for invasive disease. Histopathological diagnosis, by examining the lung tissue by biopsy remains the gold standard.5 Pulmonary haemorrhage sometimes occurs in the presence of large cavitating nodules or consolidations located close to larger pulmonary vessels. Sometimes clinical and radiological worsening with or without pulmonary hemorrhage may be seen with neutrophil recovery, this has been referred to as immune reconstitution inflammatory syndrome and does not require change in therapy. It is related to recovery of innate immunity and release of proteolytic enzymes from neutrophils which are responsible for lung tissue destruction with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse.6 Our patient developed the typical features of immune reconstitution inflammatory syndrome characterized by radiological deterioration and massive hemoptysis following recovery of neutrophils. When invasive aspergillosis involves large vessels, outcomes are almost invariably dismal.

Conclusion

Invasion of large vessels by aspergillus, in immunocompromised patients, portends a poor prognosis despite aggressive and appropriate management. Antifungal therapy may be able to limit the spread of infection to some extent but recovery of neutrophils is the most important parameter reflecting improved outcome, even though neutrophil recovery may itself be
associated with immune reconstitution inflammatory syndrome which is very well highlighted in this case. Survival of leukemia patients, to a large extent, depends on their ability to overcome complications of invasive aspergillosis, and this is the greatest challenge to the physician treating such patients.

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References


