



Case report

Successful management of pulmonary hemorrhage and aspergillosis in a patient with acute myeloid leukemia (AML-M3)



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ABSTRACT

A 35-year-old man presented with a one month history of gingival bleeding. He was diagnosed with Acute Myeloid Leukemia (AML-M3). During treatment he developed alveolar hemorrhage for which he was treated with a steroid. After the steroid treatment he developed a nodule, a cavitory lesion and atelectasia in the left lung. He was treated with voriconazole. After therapy with voriconazole his lesion significantly decreased. This case illustrates the efficacy and safety of antifungal therapy with voriconazole for aspergillosis complicated by AML.

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1. Introduction

Acute myeloid leukemia (AML) is a hematopoietic neoplasm of the myeloid line of blood cells. Acute Promyelocytic Leukemia (APL) is a biologically and clinically distinct form of AML. APL is rarely seen in the first decade but increases with the second decade and into early adulthood [1]. APL patients present with symptoms such as pancytopenia, fatigue, infection, bleeding gums, bleeding, nosebleeds and disseminated intravascular coagulation [2].

Hematological malignancies are associated with many opportunistic infections including invasive aspergillosis (IA), an important destructive fungal infection [3]. IA complicates 5–29% of the cases of Acute Myeloid Leukemia (AML), and the risk is correlated with the degree of immuno-suppression following chemotherapy [3–5].

Voriconazole is a triazole derivative which is frequently used due to its potency, broad spectrum activity, clinical efficacy, safety and tolerance [6,7]. Numerous case studies and randomized control trials have shown that voriconazole is superior to amphotericin B in the treatment of IA and it is now considered the first-line therapy in

many treatment centers [8].

Below we present a case of AML-ML complicated by invasive aspergillosis treated with voriconazole.

2. Case report

A 35-year-old man presented with a one-month history of fatigue and gingival bleeding. Physical examination of the patient revealed hepatomegaly. Complete blood count (CBC) showed low counts with peripheral blasts. Subsequent bone marrow examination and immunophenotyping confirmed the diagnosis of Acute Myeloid Leukemia (AML-M3), but the patient refused treatment. Fifteen days later, the patient was admitted to hospital with deterioration of his overall condition. He received induction chemotherapy with All Trans Retinoic Acid (ATRA), cytarabine and idarubicin. On the thirtieth day of chemotherapy, chest pain, dyspnea and hemoptysis occurred. Results of laboratory examination were as follows: Hemoglobin: 8.5 g/dL, WBC: $1.4 \times 10^9/L$, Platelets: $60 \times 10^9/L$, PT 16 s, APTT: 26 s, INR of 1.3. On chest X-rays, ground glass opacities were seen in both lungs. In the parenchymal window on the thorax CT, diffuse bilateral pulmonary alveolar hemorrhaging combined with patchy opacities were observed (Fig. 1). The patient's condition was diagnosed as ATRA-dependent alveolar hemorrhage and steroid treatment was begun (Dexametazon 2×10 mg/day). About 15 days after initiation of steroid treatment, coughing and release of sputum started. On chest CT scans, in the

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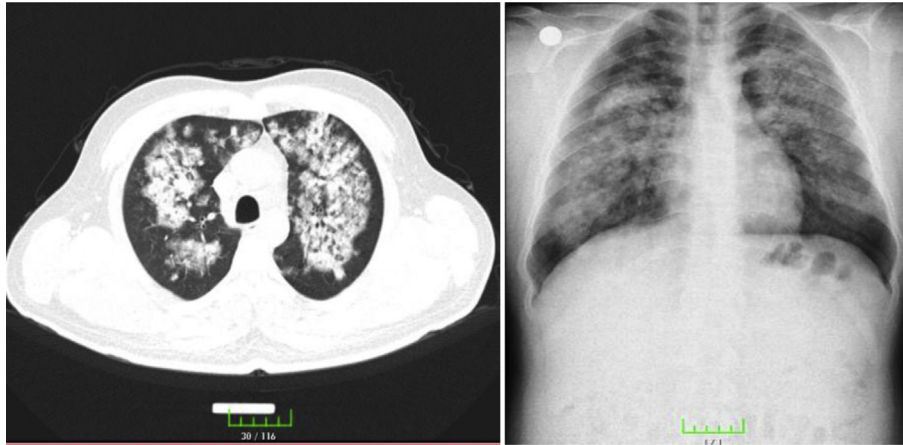


Fig. 1. Alveolar hemorrhage after treatment of ATRA.

parenchymal window, a thick-walled peripheral ground-glass cavitary lesion approximately 27×18 mm in size was observed in the left upper lobe. In the left lower lobe mediobasal segment, an atelectasis 7.5×4.5 cm in size was found, and in the right lower lobe irregular nodules from 10 mm to 16 mm in size of the area were observed (Fig. 2). Bronchoscopy was performed and bronchial lavage taken. Tuberculosis culture and galactomannan were negative. Serial galactomannan antigen tests on the patient's blood were performed. After 20 days galactomannan was positive and treatment with voriconazole was started (Table 1). One month later under voriconazole treatment, the left upper lobe cavitary lesion and lower lobe atelectasis were found to have significantly decreased (Fig. 3). The patient is still being monitored in our clinic.

3. Discussion

Differentiation syndrome (DS), previously known as retinoic

acid syndrome, is the main life-threatening complication of therapy with differentiating agents [either trans retinoic acid (ATRA) or arsenic trioxide (ATO)] in patients with acute promyelocytic leukemia (APL) [9]. Abnormal findings in chest radiography or computerized tomography are very common during the course of DS [10]. The typical findings on a chest radiograph are interstitial infiltrates (i.e., septal lines and peribronchial cuffing, ground glass opacity) and pleural effusion. An increased cardiothoracic ratio (up to 87%) and parenchymal consolidation are also frequently encountered (47%), with or without air bronchogram [11]. Also, congestive heart failure and pneumonia in a febrile neutropenic patient should be excluded from this pattern. In such cases ecocardiography, microbiologic isolates, patterns of fever, further response to intravenous dexamethasone or antibiotics, and the clinical and radiological course will aid in diagnosis. Notably, an association between the occurrence of DS and disseminated intravascular coagulopathy and haemorrhagic syndrome, including

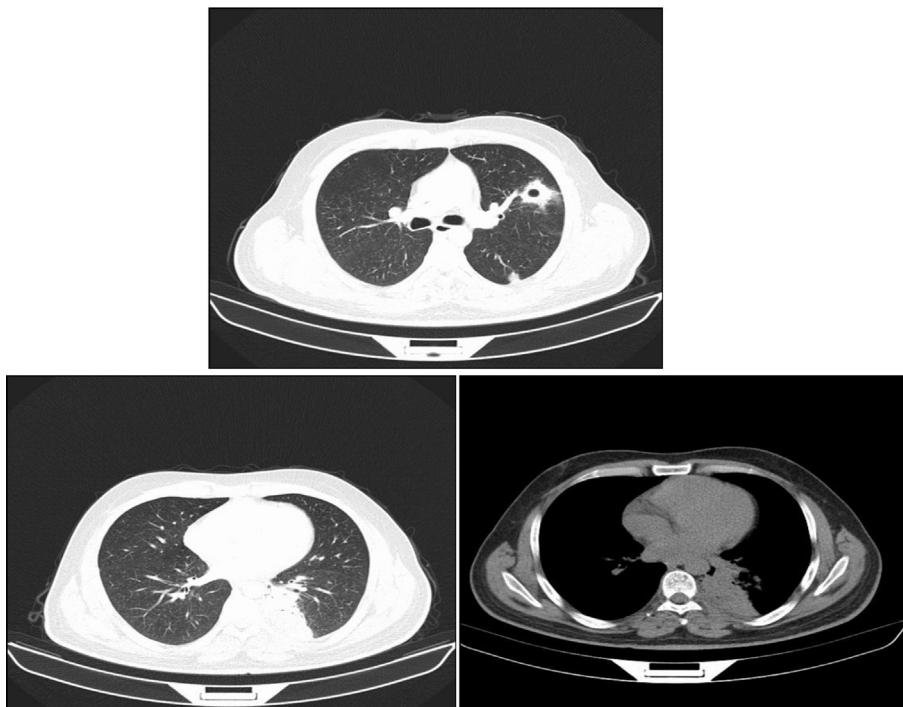



Fig. 2. Before treatment.

Table 1
Prognosis scheme during treatment.



	June 17	June 30	August 01	September 25	October 16	November 07
Clinical History	Hospital admission Fatigue, bleeding gum	Intensive care unit	Hemoptysis dyspnea	Cough sputum		
Treatment	Refused treatment	ATRA cytarabine idarubicin			Voriconazole started	
Diagnosis			Widespread patchy opacities	Left upper lobe cavitary lesion, left lower lobe atelectasis		Cavitary lesion disappeared, atelectasis decreased
				Negative GM antigen test on blood	Positive GM antigen test on blood	
			ATRA dependent alveolar hemorrhage	BAL; normal cytology		

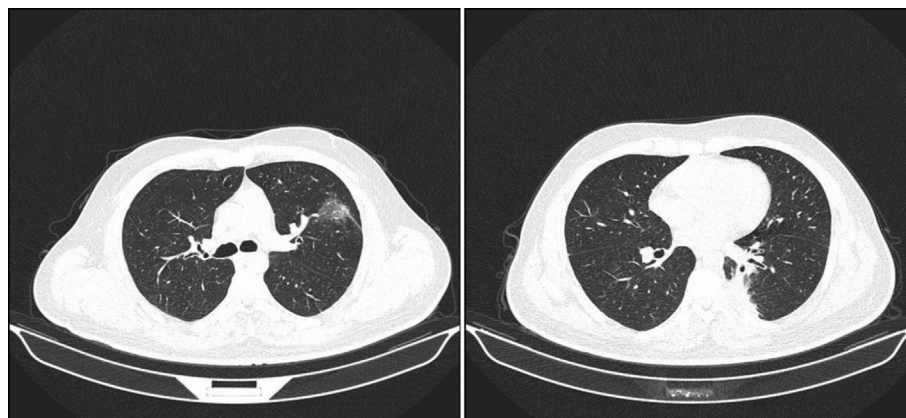


Fig. 3. After treatment.

pulmonary bleeding, has been reported [10,12]. These findings suggest that, at least in some cases, DS and pulmonary hemorrhage may occur concomitantly as part of the same pathogenic process.

It was thought that pulmonary hemorrhage was rarely a complication of ATRA; when our patient presented accordingly, ATRA treatment was stopped and steroid treatment was started. After two weeks of symptoms the patient partially regressed but new radiological abnormalities occurred.

Invasive aspergillosis (IA) is an infection frequently found in AML patients undergoing induction chemotherapy. Both acute infection and relapse are particularly associated with severe neutropenia, the use of broad-spectrum antibiotics or high-dose corticosteroids. IA patients have a higher risk of reactivation of the infection with further chemotherapy, probably due to the fact that fungal organisms remain viable in the initial lesions [13]. Patients

with acute leukemia and a history of previously treated IA on additional chemotherapy are at an approximately 50% risk for recurrent invasive aspergillosis. Due to the higher benefit-risk ratio it is universally accepted that IA is not an absolute contraindication for further chemotherapy [14–16]. The diagnosis of invasive aspergillosis may be difficult to confirm. One of the problems in diagnosing invasive pulmonary aspergillosis is that the isolation of *Aspergillus* from respiratory secretions or its presence on a Gram stain preparation may be misleading, because the fungus can be a colonizing organism or the result of laboratory contamination as well. The diagnosis of invasive aspergillosis requires presence of the fungus in tissue specimens. Also, *Aspergillus* infection should be confirmed by culture, since it cannot be diagnosed with certainty by microscopy. Many patients with documented invasive aspergillosis have negative cultures. This has been observed in

surveillance studies, and the prevalence of negative cultures varies depending on the population being evaluated. As an example, in multicenter surveillance studies, only 25 to 50% of hematopoietic cell transplant recipients who met criteria for invasive aspergillosis based upon galactomannan antigen results had positive cultures [17,18].

Radiological imaging remains the cornerstone with the “halo” sign and “crescent” sign on CT scans being regarded as diagnostic for invasive pulmonary aspergillosis. Pulmonary aspergillosis typically manifests itself as single or multiple nodules with or without cavitation, patchy or segmental consolidation, or peribronchial infiltrates with or without tree-in-bud patterns. One relatively large review noted that small nodules (<1 cm) were most common (20 of 46; 43%), followed by consolidation (12 of 46; 26%), large nodules (masses, 10 of 46; 21%), and peribronchial infiltrates (4 of 46; 9%) [19]. Another large study that included neutropenic and nonneutropenic patients showed that the more specific signs (nodules and cavitation) were infrequent, with principal radiographic findings including consolidation, ground-glass infiltrates, and pleural effusions [20]. In febrile neutropenic patients, systematic CT scans allow earlier diagnosis of IPA [21]. Definitive diagnosis depends on tissue biopsy, which may not be feasible, depending on the degree of cytopenia and coagulation abnormalities in such patients.

Antifungal therapy remains the mainstay of treatment for invasive aspergillosis [22]. However, the combination of antifungal treatment and surgical resection has been shown to dramatically improve the prognosis of IA. Aggressive surgical resection has been associated with improved outcome by eliminating macroscopic foci of IA that could complicate subsequent immunosuppressive chemotherapy; although due to the fact that IA is a multifocal disease at least at microscopic level, even surgical excision does not guarantee a complete cure [23]. The risk of leukemia relapse or the presence of multiple and bilateral lesions does not allow for the surgery. Thus secondary antifungal prophylaxis is the main option for such patients [10]. Voriconazole is a new broad spectrum triazole that is active in vitro against various yeasts and molds, including aspergillus species. Recent data [24] show better responses (52.8 vs. 31.6% at 12 weeks), improved survival (70.8 vs. 57.9%) and fewer side effects with voriconazole compared to the standard approach of initial therapy with amphotericin B. Treatment failures after use of liposomal amphotericin B have been successfully treated with voriconazole [25,26].

In this case report, a high-risk acute myeloid leukemia patient underwent chemotherapy and steroid treatment after alveolar hemorrhage aggravated by a fungal infection. A well-tolerated and successful treatment with voriconazole decreased the pulmonary cavity and infiltration. Nevertheless, it should be noted that the observation periods for our case and also for those reported in the literature are relatively short.

In conclusion, ATRA-induced pulmonary hemorrhage is a rare complication. This needs to be kept in mind as a potential complication. If it does not respond to first-line treatment, infectious causes such as invasive aspergillosis should be considered, and treatment should be started early.

Conflict of interest

All authors have no conflict of interest to disclosure.

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