Aspergillus Vegetative Endocarditis Complicated with Schizocytic Hemolytic Anemia in a Patient with Acute Lymphocytic Leukemia

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Abstract. Aspergillus vegetative endocarditis developing in a patient with acute lymphocytic leukemia during the phase of hematological remission has led to a fatal outcome, complicated with severe hemolytic anemia with red cell fragmentation. Systemic aspergillosis may involve heart valves with underlying disorders, but seldom affects intact valves even in severely compromised hosts. Among such rare cases so far reported, only 2 cases have been documented in acute leukemia, despite a huge prevalence of pulmonary and systemic aspergillosis in hematological malignancies. Our present case is essentially the same as in the preceding two cases in that endocarditis occurred during the hematological remission. These clinical observations may suggest that every leukemic patient suffering from aspergillosis is susceptible to the valvular complication after, rather than during, the period of severe myelosuppression, because platelets play an important role in the formation of thrombotic lesions.

Introduction

Among the opportunistic fungi, the most common cause of pneumonia is Aspergillus sp. [1]. As a result of hematogenous dissemination, the myocardium may be involved in systemic aspergillosis, but the valvular endocardium is seldom affected even in highly immune-compromised hosts unless they have underlying valvular disorders [2-11].

In this case report, we describe an unusual complication of Aspergillus vegetative endocarditis which occurred in a patient with acute lymphocytic leukemia (ALL) during the phase of hematological remission. This article also deals with the pathogenesis and predisposing factors of this rare but fatal complication.

Case Report

A 68-year-old male with ALL, L1 category of FAB classification, was admitted to our hospital in early January 1985. He became feverish 3 weeks after receiving a regimen with vincristine and prednisolone. Broad-spectrum antibiotic treatment was initiated (cephems and aminoglycosides during the entire course of his illness), but the fever persisted and a chest X-ray revealed bilateral pulmonary infiltrates. Intravenous amphotericin B (AMP, total dosage 514.5 mg) was then initiated, together with oral 5-fluorocytosine, to reduce the dosage of AMP because of his intolerance of the toxicity. But the fever persisted until the patient achieved a complete remission. Although the pulmonary shadow was not remarkably improved, the AMP was discontinued for 1 week because of a suspect of its hepatic toxicity. On 8th April 1985, a high fever recurred and a new systolic murmur became audible at the cardiac apex region, when the two-dimensional (2-D) echocardiography detected only mitral regurgitation without any apparent vegetative lesions in every valve. Myocardial infarction was considered unlikely since the electrocardiogram and the serum level of creatine kinase remained unchanged. The murmur became louder with symptoms of anemia and thrombocytopenia developing. Despite the reinstitution of AMP, the condition was further deteriorated and resulted in an occurrence of hemoglobinuria and fragmented erythrocytes on blood smears. He became unconscious and died on 15th April 1985. During the terminal course, no hemostatic data suggested disseminated intravascular coagulation. Postmortem examination showed a pair of vegetative masses on the mitral valve (fig. 1), which had not been detected by our reviewing the videorecord of a 2-D echocardiography performed one week prior to his death. The microscopic study revealed that the vegetation consisted of a thick sheet of septate branching hyphae infiltrating the thrombotic masses and valvular endocardium. Similar organisms were
also found in the myocardium and lungs. Although no organism grown from these affected lesions, the causative agent was immunohistochemically [12] identified as *Aspergillus* sp. The bone marrow showed normal architecture, indicating that he had complete remission. Thromboembolism was absent in any organ examined, including brain and kidneys, histologically excluding a possibility of thrombotic thrombocytopenic purpura.

**Discussion**

A pair of firm and rigid vegetative masses were formed on each leaflet of mitral valve in a patient with ALL during the phase of hematological remission. These invasive lesions affected by *Aspergillus* sp. could well bring the sudden appearance of heart murmur followed by the development of hemolytic anemia at the terminal course of this patient. This causative organism seated in the left-sided heart valves was presumably disseminated from the primary lesions in situ despite the antifungal chemotherapy.

Schizocytic hemolytic anemia comprises two categories, microangiopathic hemolytic anemia (MIHA) and macroangiopathic hemolytic anemia (MAHA) [13]. Since this case showed no histological evidence of MIHA, we considered a possibility of MAHA, which is usually associated with disordered heart valves or with cardiac surgeries [13]. In contrast, valvular lesions in infective endocarditis very rarely cause hemolytic anemia [14]. In our patient, a rapid growth of vegetative lesions might have given rise to a rapid progression of turbulence of blood flow to cause MAHA [14], since our 2-D echocardiography performed one week prior to his death failed to detect such apparent lesions as found at autopsy. Alternatively, the physical property of rigid valvular lesion [15] might be also related to this unusual hemolytic manifestation.

In general, air-borne spores of *Aspergillus* sp. initially colonize in the lung of compromised hosts and may result in a hematogenous dissemination [1]. The myocardium is not infrequently involved in generalized aspergillosis, but an intact valvular endocardium is seldom affected even in patients with severe underlying conditions [1, 11]. Although such rare examples of *Aspergillus* endocarditis affecting normal heart valves [2-10] have been so far reported, only 2 out of 16 cases are documented in acute leukemias [6, 9], whose incidence appears unproportionately low in view of a huge prevalence of pulmonary and systemic aspergillosis associated with hematological malignancies [16]. The rarity of valvular complications also holds true with disseminated candidiasis in acute leukemias [17].

More interestingly, all the reported cases including ours were infected with *Aspergillus* at the nadir period, before developing vegetative lesions during the time of hematological remission [6, 9]. Considering that platelets act as one of the major components to form thrombotic lesions, the infrequent occurrence of endocarditis in acute leukemia patients could be attributed, as Mikulski et al. [6] indicated, to a marked thrombocytopenia during the myelosuppression, in which granulocytopenia apparently renders the patient especially susceptible to fungal infection.

With the improvement of current anti-leukemic chemotherapy and supportive therapy, the number of patients who are susceptible to fungal infection has been paradoxically increasing [1, 18]. In other words, cardiac complication would also gain a high incidence in future. However, as this report suggests, once fungal endocarditis occurs, even an extensive use of antifungal agents other than a surgical removal does not seem to have a curative effect [13]. Physicians must be aware that such fatal endocarditis may de-
velop after, rather than during, the period of severe myelosuppression in leukemic patients.

References


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