Invasive aspergillosis in a systemic lupus erythematosus patient

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Systemic lupus erythematosus (SLE) is an autoimmune disease with a broad clinical manifestation characterized by production of antibodies against cellular nuclear components. The prevalence of SLE among many countries is variable, ranging from 2.9 to 400 per 100,000. In Cipto Mangunkusumo General Hospital, the incidence of SLE between 1990 and 1998 is 37.3 per 10,000 hospitalization.[1]

Patients with autoimmune disease have at least twofold risk of acquiring infections compared with healthy individuals. This may be due to the immunosuppresant therapy but could also caused by the primary immune dysregulation that was the basis for the pathogenesis of their disease, or other autoimmune disease manifestations such as lymphopenia.[2] Infection is the main factor increasing the mortality and morbidity of SLE patients. A study in New York conducted between 1966 and 1976 involving 223 SLE patients reported 150 cases of infection, of which 23 were opportunistic infection: 12 were candidiasis while 11 others were deep fungal infection. The use of corticosteroids in SLE is the main factor that predispose patients to infection, particularly fungal infection.[3]

Aspergillosis is the term used to denote all disease caused by any one of the pathogenic and allergenic species of *Aspergillus*. The annual incidence of aspergillosis in the United States is reported to be 1–2 per 100,000.[4] *Aspergillus fumigatus* is the cause of most cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes. The mortality rate of invasive aspergillosis is 50% when properly diagnosed and treated; otherwise it could be as high as 100%.[5]

CASE REPORT

A 21-year-old woman presented with one-week history of throbbing headache. The pain, which radiated to the upper molar, was intermittent at first but had been gradually increasing in intensity and eventually became constant. The pain was not relieved by analgesics such as paracetamol or mefenamic acid.

The patient was diagnosed with SLE 4 years earlier and had since had regular follow-ups at the rheumatology clinic at our institution. She was treated with methylprdnisolone 16 mg t.i.d. and mycophenolate mofetil (MMF) 500 mg b.i.d.

Four months prior to the admission, she began to notice enlargement of her left eye, which became gradually increasing in size, accompanied with mild and intermittent pain. She also experienced diplopia and a decrease in visual acuity of her left eye, but there was no complain of floaters. The ophthalmologist who examined her at that time suspected a neurological problem of the extraocular muscles of her left eye, and she was subsequently hospitalized for further investigations.

Head magnetic resonance imaging (MRI) conducted at that time revealed left maxillary, left frontal, and left ethmoid sinusitis. Three weeks after the MRI, the patient underwent head computed tomography (CT) scan, which showed left retrobulbar mass infiltrating the medial rectus and inferior rectus muscle of the left eye and roof of the left maxillary and left ethmoid sinus with destruction of the inferior orbital rim (figure 1A).

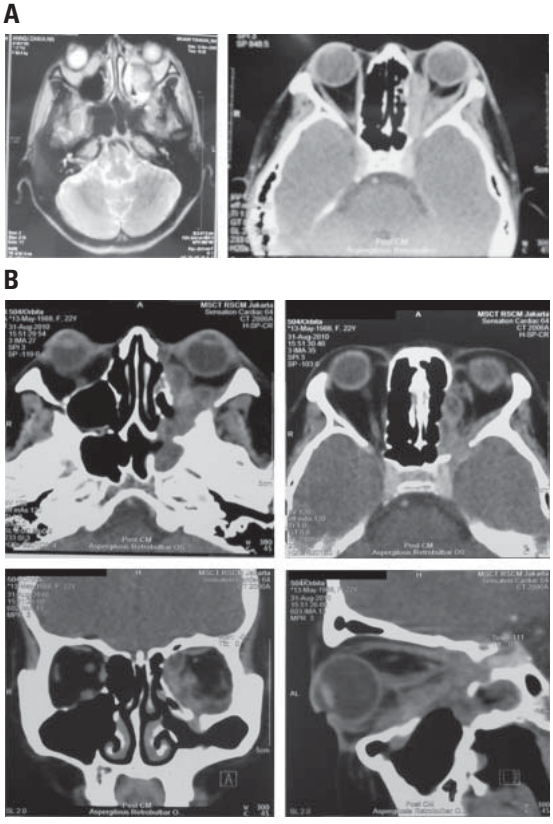

Figure 1 Head computed tomography of the patient at the time of admission (A) and after the administration of voriconazole (B).

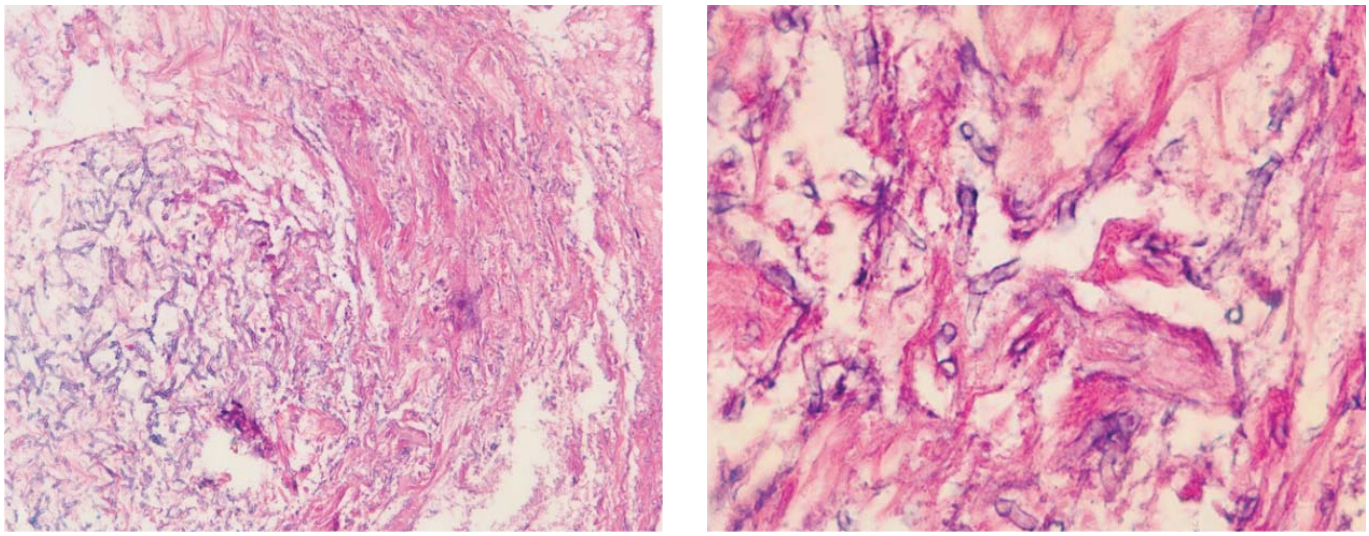

Figure 2 *Aspergillus* sp. hyphae in retrobulbar biopsy specimens. Original magnification 200 × (left), 1000 × (right).

Three months prior to the admission, the patient began experiencing throbbing headache, which radiated to the upper molar and accompanied with nausea and vomiting. Since then she also had 15 kg decrease in body weight.

With suspicion of a tumor, the patient had a nasopharyngeal biopsy, which at that time only showed chronic sinusitis. A retrobulbar biopsy guided by nasoendoscopy conducted one week before the admission showed large necrotic areas containing *Aspergillus* hyphae (figure 2). There were also found fragments of granulation tissue and blood clots resembling the histopathological feature of aspergillosis.

Physical examination at the time of admission showed a blood pressure of 100/70 mmHg, pulse rate of 84 beats/min with good pulse volume, and respiratory rate of 16 breaths/min. Her body weight and height was 48 kg and 158 cm, respectively, with BMI of 19.27 kg/m^2. On eye examination we found proptosis, erythema, and edema of the left eye. There was no supra- or infraorbital tenderness.

Laboratory examination revealed anemia with hemoglobin of 10.3 g/dL, mean corpuscular volume of 76 fL, mean corpuscular hemoglobin of 25 pg, and mean corpuscular hemoglobin concentration of 33 g/dL; hematocrit was 32%, leukocyte count was 9.9 × 10^3/mm^3 (differential count: basophils 0%, eosinophils 0%, stabs 2%, segmenters 85%, lymphocytes 13%, and monocytes 0%), platelet count was 422 × 10^3/mm^3. Serum ureum level was 37 mg/dL (normal value <50 mg/dL), serum creatinine was 0.5 mg/dL (normal value 0.6–1.2 mg/dL), aspartate aminotransferase (AST) was 19 IU/L (normal value <27 IU/L), alanine aminotransferase (ALT) was 12 IU/L (normal value <36 IU/L), albumin was 3.8 g/dL, random blood glucose was 99 mg/dL, sodium was 139 mEq/L, potassium was 3.8 mEq/L, and chloride was 103 mEq/L. Complement component (C)3 and C4 was 95.40 mg/dL (normal value 90–180 mg/dL) and 39 mg/dL (normal value 10–40 mg/dL), respectively. Anti–double-stranded DNA (anti-dsDNA) was 1061 IU/mL (normal value 0–100 IU/mL). Her chest radiograph and electrocardiograph were unremarkable.

The patient's diagnoses at the time of admission were chronic headache; retrobulbar aspergillosis; SLE with renal, hematological, and musculoskeletal involvement; and microcytic hypochromic anemia.

The patient was treated with tramadol 1 amp diluted in 500 mL of normal saline infused intravenously over 8 hours, paracetamol 750 mg, ibuprofen 200 mg, amitriptyline 5 mg, diazepam 1 mg, diclofenac sodium 50 mg t.i.d, MMF 500 mg b.i.d, methylprednisolone 4 mg t.i.d, calcium hydrogen phosphate 500 mg and cholecalciferol 133 IU t.i.d., folic acid 1 tab t.i.d., lansoprazole 30 mg q.d., and sucralfate syrup 5 mL t.i.d.

For the aspergillosis, she was treated with amphotericin B with a dose of 5 mg/day, which was gradually increased (5 mg/day) until a dose of 0.5–1 mg/kg body weight/day. After 14 days, the treatment was continued with oral itraconazole 400 mg q.d.

After one month of hospitalization, the headache and orbital edema had improved. The patient was thus discharged with outpatient follow-up and instruction to continue therapy with itraconazole 400 mg q.d., MMF 500 mg b.i.d., and methylprednisolone 8 mg t.i.d. At the time of discharge, she was in good condition with stable hemodynamics.

Magnetic resonance imaging at the end of the hospitalization showed malignant mass in the left retrobulbar area, which infiltrated the medial and lateral rectus muscle, left distal optic nerve, and left maxillary sinus. There were also left maxillary, ethmoid, and sphenoid sinusitis. Intracerebral area showed no abnormalities.

Two weeks after being discharged, the patient was rehospitalized because her headache, now worse than before, and left eye swelling had recurred. Laboratory examination results at that time were as follows: hemoglobin 8.7 g/dL, leukocyte count 22.43 × 10^3/mm^3, platelet count 271 × 10^3/mm^3, erythrocyte sedimentation rate 6 mm/hr, anti-dsDNA 370.5 IU/mL, C3 80.04 mg/dL, C4 39.36 mg/dL, antinuclear antibodies was positive at 1:3200 dilution with speckled and centromere pattern; aspartate aminotransferase was normal (29 U/L), but there was an increase in ALT level (167 U/L);

serum ureum 36 mg/dL, serum creatinine 0.3 mg/dL, IgM anticardiolipin antibodies (ACA) 5.3, IgG ACA 6.8, IgM β2-glycoprotein I (β2GPI) 3.9, IgG β2GPI 1.9. Hemostasis: prothrombin time 13.1 sec (1 × control; normal value 9.8–12.6 sec), activated partial thromboplastin time 36.2 sec (1 × control; normal value 31.0–47.0 sec), and international normalized ratio 1.18.

Electroencephalography showed slow activity in the bilateral (predominantly left) frontal area. Diagnosis of the Department of Neurology was paraparesis ec. corticosteroid-induced myopathy. Referral to the Department of Ophthalmology returned with these results: proptosis of the left eye; visual acuity was >3/60 (right eye) and 0.5/60 (left eye); the anterior segment of both eyes and fundus of the right eye was normal but there was optic nerve head atrophy of the left eye; intraocular pressure of the right and left eye was 15.5 and 13, respectively. Head CT scan showed left retrobulbar mass filling the sphenoid, ethmoid, and left maxillary sinus, with infiltration of rectus muscles of the eye, apical segment of the left optic nerve, and intracranially into the left parasellar area.

Due to the deteriorated condition of her left eye, the patient was planned to undergo left orbital exenteration. However, her family did not consent to the plan; so we decided to administer an alternative treatment course of intraconal irrigation of amphotericin B 2.5 mg (25 mL) for 10 days. Before the initiation of treatment, we performed biopsy to obtain specimen for culture and resistency test.

On day 9 of the amphotericin B treatment, the patient developed fever. On physical examination we found a temperature of 38.1°C with normal pulse rate (96 beats/min). Laboratory examination revealed leukocytosis (18.28 × 10^3/mm^3); C-reactive protein was 51.4 mg/L and procalcitonin was >5 µg/L. She was diagnosed with sepsis ec. left orbital cellulitis. Amphotericin B was substituted with itraconazole 400 mg q.d. and meropenem 1 g t.i.d. for 14 days. Blood and pus cultures showed *Aspergillus fumigatus*, which in susceptibility test showed sensitivity to voriconazole and amphotericin B (with dose adjustment), and resistant to itraconazole. It was thus decided to administer intravenous voriconazole 300 mg b.i.d. on the first day continued with a dose of 200 mg b.i.d. for 10 days. At day 10 her treatment was continued with oral voriconazole 200 mg b.i.d. for 4–6 weeks.

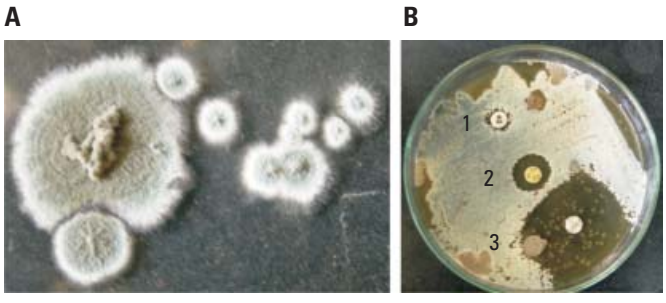

Figure 3 Results of blood and pus cultures: (A) colonies of *Aspergillus fumigatus*; (B) susceptibility test showed resistance to itraconazole (1) and sensitivity to amphotericin B (2) and voriconazole (3).

Computed tomography after the administration of voriconazole showed pathologically enhanced heterogeneous lesion with air component in the left retrobulbar (intra- and extraconal) area infiltrating the rectus and oblique muscles of the eye and left optic nerve, with destruction of the ethmoid, sphenoid, inferior orbital wall and sphenoid wing, extending intracranially into the left parasellar area, and filling the left ethmoid, left maxillary, and sphenoid sinus (figure 1B). There was significant reduction of the mass in comparison with the previous CT. There was also left buccal cellulitis suggestive of fungal infection. The Department of Radiology confirmed the presence of intracranial infiltration; however, the intracerebral area in cavernous sinus was still intact.

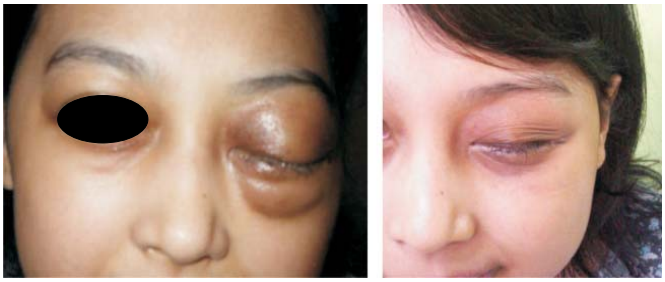

Figure 4 Condition of patient's left eye at the time of rehospitalization (left) and 4 weeks later (right).

After 4 weeks of hospitalization, the symptoms of headache and orbital edema had improved, although the vision loss of her left eye was permanent. Laboratory results were normal; ALT had decreased to 52 U/L, and was 7 U/L in a follow-up examination one month later. The patient's lupus activity was also under control.

DISCUSSION

Systemic lupus erythematosus is a multisystem disorder caused by production of immune complex-forming autoantibodies and complement resulting in tissue damage.[6] Infection is the main cause of morbidity and mortality in SLE patients, whose dysfunction of immune system is considered to play a role. Besides, administration of steroids and other immunosuppressive agents also contribute to the increased susceptibility to infection.[3] Our patient, who was diagnosed with aspergillosis of the retro-orbital area and paranasal sinuses, had suffered from SLE and received long-term steroid and immunosuppressive medication, rendering her vulnerable to opportunistic infections.

Aspergillus sp. is very common in the environment. This group of fungi has hyaline (nonpigmented), septate, and branching hyphae that give rise to numerous conidia (spores). *Aspergillus fumigatus* is the most common cause of invasive aspergillosis.[5] The main risk factors are severe neutropenia and the use of corticosteroids, although this disease can also occur in individuals without those conditions. The risk of invasive aspergillosis and mortality associated with this disease are also increased with longer duration and higher dose of corticosteroids. The incubation period varies between 2–90 days.[5,7,8]

The initial presentation of our patient was a condition called orbital apex syndrome, a group of rarely encountered symptoms consisting of ophthalmoplegia, ptosis, and vision loss. Several conditions that can cause orbital apex syndrome are malignancy, inflammation, or, as in our case, infection. Because of its poor prognosis, diagnosis must be made early, especially when there is evidence of immunodeficiency risk factors.[9–11] Unfortunately, due to the posteriorly located mass at the orbital apex, the diagnosis of our patient was made 4 months after the development of initial symptoms.

Sinus involvement occurs in 5–10% cases of invasive aspergillosis. Other than fever, common symptoms are uncomfortable sensation in the nose or face, nasal congestion, and rhinorrhea, which sometimes are accompanied with blood. Asymmetric and swollen face, epistaxis, proptosis, cranial nerve abnormalities, and bone erosion are suggestive of fungal infection. Computed tomography or MRI are important diagnostic procedures but they lack the ability to distinguish between sinusitis caused by invasive aspergillosis and other forms of sinusitis, such as allergic, bacterial, or other fungal sinusitis.[5,9]

Definitive diagnosis is made when one of the following is found: (1) positive culture of samples obtained from the affected lesion (e.g. brain abscess); or (2) positive histological examination and culture from samples obtained from the affected organ (e.g. sinus or skin). In our case, the patient had positive culture and showed histological feature of invasive aspergillosis.

Diagnosis of invasive aspergillosis can also be made by detection of galactomannan antigen or β-D-glucan; both are components of fungal cell wall. Galactomannan antigen is more specific in diagnosing invasive aspergillosis, while β-D-glucan may be detected in other invasive fungal infections. A meta-analysis showed that serum galactomannan antigen test has sensitivity and specificity of 71% and 89%, respectively. Histopathological examination may reveal area of infarction, invasion of hyphae into the blood vessels, or acute necrosis with limited inflammation. *Aspergillus* hyphae could be characterized as hyaline, narrow, septate, and dichotomously branching hyphae.[9]

Culture is important in confirming the diagnosis of aspergillosis, since there are only very few other species of fungi that have similar histological features. Fungal growth medium is more sensitive than bacterial medium. From all cases of invasive aspergillosis, only 10–30% show positive culture, and about 40% are only diagnosed at autopsy.[5,9]

Several antifungals have been known to be effective in treating invasive aspergillosis, such as voriconazole, itraconazole, posaconazole, caspofungin, micafungin, and amphotericin B. Voriconazole is the first line agent, while caspofungin, posaconazole, and amphotericin B lipid complex are second line agents. Intravenous administration is usually preferred in invasive aspergillosis. Duration of treatment varies from 3 months to several years, depending on host immunity and treatment response. Recurrence of infection may happen if there is suboptimal response to treatment or defective immune system.

Due to several limitations, our patient did not receive voriconazole as her treatment. It was then decided to give her amphotericin B as an alternative, administered both intravenously and locally (as intraconal irrigation). Amphotericin B exhibit fungicidal activity. Its potency depends on serum concentration and pathogen susceptibility. Amphotericin B may be administered intravenously, topically, or, in cases of ophthalmic infection, intravitreally and intracamerally.[12–14] Reported adverse effects of amphotericin B include cardiac arrhythmia, acute kidney injury, and anemia.[15,16]

After 14 days, the treatment of our patient was continued with oral itraconazole. Itraconazole is the oral agent of choice for treating chronic and allergic form of aspergillosis. It is one of the azole derivatives, which exert their fungicidal activity by inhibiting cell growth, resulting in cell death. Except fluconazole, all of the azole derivatives may lower the immune system; thus they may reduce inflammation, although this effect will also decrease their activity. For fungal infection in orbital area, the azoles can only act as fungistatic.[12] Resistance to one or more of the azoles may occur in long-term treatment. A prospective study that collected isolate culture from several hospitals in the Netherlands had showed that the annual prevalence of resistance to itraconazole ranged between 1.7 and 6%. The study also found that the itraconazole-resistant isolates showed elevated minimum inhibitory concentration of voriconazole and posaconazole. Besides resistance, it is also important to consider potential interaction with other drugs before administering voriconazole and itraconazole.[17–19]

Culture results showed that the *Aspergillus* infecting the patient's left eye was resistant to itraconazole, and no satisfying result was obtained from the treatment with itraconazole or amphotericin B; hence readministration of voriconazole was decided. A study had showed that as initial treatment of invasive aspergillosis, voriconazole was more superior in treatment response, survival rates, and safety than amphotericin B. The adverse effect commonly found is temporary visual disturbance.[15]

Surgical intervention for invasive aspergillosis can sometimes be curative, as in some forms involving bone, heart valve, paranasal sinuses, proximal lung, large veins, and in cases of brain abscess, keratitis, and endophthalmitis.[5] Our patient did not undergo surgical treatment since her family did not consent to the orbital exenteration.

In situations where there is a medium to high risk of fungal infection, antifungal prophylaxis administration for superficial or systemic candidiasis has been widely accepted. Fluconazole and oral itraconazole have no activity against *Aspergillus* sp., and itraconazole solution show only medium efficacy; posaconazole solution may be more effective. Some data supports the use of low-dose intravenous micafungin. In general, there has not been yet truly effective prophylactive regimens.[5]

In invasive aspergillosis, cure is possible if there is improvement of the immune system, while the allergic and chronic form is generally incurable. Mortality rate of invasive aspergillosis is 50% when properly diagnosed and treated;

otherwise it could be as high as 100%. A case report described a fatal case of aspergillus sinusitis, in which the infection had spread intracerebrally.[5,20] One of the factors that improve our patient's chance of survival was that there was no intracerebral extension of the infection.

In summary, corticosteroids and immunosuppressants treatment in SLE predispose patients to fungal infection, including invasive aspergillosis, which is caused by a group of fungi called *Aspergillus*. This disease is known to have poor prognosis, high recurrence rates, and there has not been yet prophylaxis with proven efficacy. Diagnosis of aspergillosis often presents challenges to the clinicians. There are various regimens in treating fungal infection, depending on the etiology and severity of infection. Voriconazole has become the treatment of choice in severe *Aspergillu*s infection, followed by amphotericin B. Resistance to antifungal drugs has been reported, resulting in high recurrence rates. In invasive aspergillosis, surgical intervention can be considered and sometimes is curative.

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