CASE REPORT

Fungal Mycotic Aneurysm in a Case of Acute Lymphoblastic Leukemia

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Abstract We report a case of a 15-year old boy who was managed as a case of B cell lymphoblastic leukaemia with the modified BFM 90 protocol. During the induction phase, he developed febrile neutropenia with sino-pulmonary fungal infection confirmed on histopathology. He developed left sided hemiparesis during in-hospital management of febrile neutropenia. Neuroimaging revealed 9.6×8.4 mm round well defined aneurysm arising from right cortical artery in distal middle cerebral artery territory. He underwent fronto-temporo-parietal craniectomy with evacuation of the hematoma and excision of the aneurysm. Histopathological examination of excised aneurysmal specimen grew same species of fungus as was cultured from nasal scraping. He recovered fully in next 6 months with minimal residual focal neurological deficits. Presently he is in maintenance phase chemotherapy. We presented this case to illustrate a rare complication of ALL therapy with mycotic aneurysm secondary to invasive fungal infection treated successfully.

Introduction

An aneurysm is an abnormally dilated arterial vessel. Term “mycotic aneurysm” refers to all infected aneurysms except for those resulting from syphilis. Term “mycotic” was

proposed by Osler in 1885 in view of the shape of the aneurysm resembling a mushroom [1]. Infected aneurysms, in contrast to their terminology, commonly develop secondary to bacterial infections. Risk factors most commonly are arterial injury, antecedent infections, immunocompromised status like in patients with cancer, HIV infection, cirrhosis, post-transplant recipients and atherosclerosis in elderly [2].

Septic embolization secondary to infective endocarditis, cellulitis and lung abscess can present with varied neurological complications like ischemic stroke, brain abscess, mycotic aneurysm and intraventricular bleed [3]. Fungal arterial infections are rare and secondary to severe immunosuppression [4, 5].

Mycotic aneurysms have rarely been reported to be associated with hematological malignancies. We present the medical course of a patient of acute lymphoblastic leukaemia with febrile neutropenia, sino-pulmonary infection and cerebral mycotic aneurysm.

Case Report

A-15-year old boy was diagnosed as a case of Pre-B cell acute lymphoblastic leukemia (ALL) in June 2012. Subsequently, he was started on modified BFM-90 protocol—four drug regimen (Prednisolone, vincristine, daunorubicin, and cyclophosphamide). In 3rd week of chemotherapy, he was admitted with the complaints of high grade fever, productive cough and nasal stuffiness of 1 week duration. On general examination, he was febrile (39 °C), found to have severe pallor, oropharyngeal congestion and maxillary/frontal sinus tenderness. Fundal examination revealed bilateral retinal hemorrhages. Systemic examination revealed coarse crepitations in right infra-scapular and infra-axillary regions; cardiac, neurological and abdominal examinations were unremarkable.

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Investigations

Haematological investigation at admission revealed pancytopenia (Haemoglobin—6.9 gm/dL, total leucocyte count—2000/ μ L with absolute neutrophil count of 200/ μ L and platelet count—7000/ μ L). Coagulation profile was normal. Radiological imaging suggested pan-sinusitis and bilateral non homogenous opacities in lung parenchyma (Fig. 1). Nasal scrapings showed fungal hyphae. Serum galactomannan was raised. Bacterial cultures were sterile. Cultures from the nasal scraping, blood and sputum received after 15 days were suggestive of aspergillosis.

Treatment Given

Patient initial management included empirical antibiotics (initially Inj. cefoperazone 1 g i/v q12 h) for febrile neutropenia, supportive care with blood components and simultaneously evaluating for possible source of infection. The antibiotics were escalated to Inj. Piperacillin–Tazobactam 2.25 g i/v q6 h on D₃ and carbapenems—Inj. Imipenem + Cilastin 1.5 g i/v q8 h on D₅ of hospitalization. Antifungal therapy with liposomal amphotericin B was added after the receipt of nasal scrapping report showing fungal hyphae on D₇. He responded clinically and had radiological improvement in lung shadows by D₂₄ (Fig. 2). He simultaneously received therapy for ALL as per modified BFM-90 protocol.

Complication During Hospital Stay and Management

During in-hospital stay, while being managed for febrile neutropenia with probable fungal infection, he developed sudden onset left sided weakness of upper and lower limbs on

Fig. 1 Chest X-ray on D₁ of hospitalisation shows bilateral non-homogenous opacities

Fig. 2 Chest X-ray on D₂₄ of hospitalisation shows improvement in the non-homogenous opacities

D₃₄ of hospitalization with no preceding headache or altered sensorium. On neurological examination, he had left upper-motor neuron type palsy of seventh nerve and left sided hemiparesis of upper and lower limbs with 3/5 grade of power.

Clinically after neurological examination and available treatment history, differential diagnosis considered at this stage were intracerebral leukemic deposits secondary to ALL or cerebral haemorrhage secondary to DIC (sepsis related) or thrombocytopenia (sepsis or chemotherapy related). Also a possibility for asparaginase therapy (part of BFM-90 protocol for ALL) induced CVT was considered.

Repeat haematological parameters revealed reversal of pancytopenia (Haemoglobin—10.6 gm/dL, total leucocyte count—9000/ μ L with absolute neutrophil count of 5000/ μ L and platelet count—106,000/ μ L). Coagulation profile was normal.

A non-contrast neuroimaging done following the onset of hemiparesis showed right temporo-parietal hemorrhage (Fig. 3a) confirmed by contrast enhanced computed tomography (Fig. 3b). CT angiography of intra-cerebral vessels confirmed 9.6 × 8.4 mm round well defined aneurysm arising from right cortical artery in distal middle cerebral artery (MCA) territory (Figs. 4, 5). 2D Echo ruled out any vegetation or thrombosis.

He underwent right fronto-temporo-parietal craniotomy along with evacuation of intracerebral hematoma and excision of aneurysm (Fig. 6). Histopathological examination of excised specimen was positive for septate fungal hyphae and fungal culture of specimen was positive for *Aspergillus flavus*. He was continued on Inj. Liposomal amphotericin B for another 25 days. He was simultaneously also managed for ALL (modified BFM-90).

His basic disease was in remission as confirmed by bone marrow biopsy. He was discharged after 59 days of hospitalization with chest radiography showing old fibrotic changes

Fig. 3 NCCT (A) and CECT (B) brain on D₃₄ showing intracranial haemorrhage in right fronto-parietal region with peri-lesional oedema with area of hyper-intensity (possibly aneurysm)

with features of mild volume loss on the right side (Fig. 7). He was advised to continue oral voriconazole 200 mg BD and levetiracetam 500 mg BD. Patient was under regular follow up. MRI brain done after 1½ year of initial presentation at this stage show resolution of haemorrhage with hemosiderin pigment deposition (Fig. 8). Patient's neurological status gradually improved with only minimal weakness in the upper and lower limbs on the affected side.

Discussion

Intracranial aneurysm can be broadly divided into two major categories-noninfected and infected. An infected intracranial aneurysm is known as 'mycotic' regardless of

Fig. 4 CT angiography shows 9.6 × 8.4 mm round well defined aneurysm arising from *right* cortical artery in the MCA territory during (A) filling and (B) washout phases in coronal and (C) sagittal sections

Fig. 5 3D-reconstruction of the CT angiography localising aneurysm to branches of *right* MCA in (A) coronal and (B) sagittal sections

Fig. 6 Repeat CT brain on D₃₇ shows postoperative status with relief of midline shift

Fig. 7 Chest X-ray on D₅₉ of hospitalisation at the time of discharge

subtype of infection, bacterial or otherwise. Infection in mycotic aneurysms can be acquired in any of the following ways (1) direct inoculation (2) contiguous infection (3) seeding of pathogen (4) septic emboli. Allen and colleagues reported one of the largest series (26 cases) of the cerebral mycotic aneurysm. Three out of 26 patients were immunocompromised (AIDS, steroid therapy for crohn's disease, chemotherapy for multiple myeloma). Most common symptoms were headache (62 %) followed by focal neurological deficits (43 %) and fever (19 %). 65 % patients had rupture of aneurysm at some point of time. Etiological work-up revealed infective endocarditis in 73 % patients as the primary infective source. Most common location of aneurysm was MCA territory followed by anterior cerebral artery and internal carotid artery. Most common pathogen isolated were bacterial (staphylococcal aureus followed by streptococcus species) [2].

In general fungal aneurysms are less common than bacterial ones. *Aspergillus* spp. are most common culprit among fungal infections, however rarely *Candida* spp, *Penicillium* spp, *Coccidioides immitis* have also been reported [6, 7]. Oderich et al. studied 43 cases of aortic aneurysm and found *Staphylococcus* followed by *Escherichia coli* as the most common bacteria's which grew on blood or aneurysmal wall cultures [8]. A single case of fungal aneurysm due to *C. immitis* was also detected in this study.

In approximately 80 % of *Aspergillus* spp. related aneurysms, dissemination occurs via haematogenous spread either from pulmonary lesion or secondary to intra-operative contamination. Other possible focus of spread could be middle ear cavity, orbit and paranasal sinuses [6]. Fungal aneurysms have tendency to arise from basilar artery or internal carotid artery as compared to bacterial one which commonly involve peripheral vessels. However, it has been seen that aneurysm secondary to meningitis or sinusitis may also be located distally [9, 10]. In the index case, sinuses can be considered as a source of fungus for respiratory as well as cerebral vessel infection. Regarding the proposed mechanism of aneurysm formation, most common explanation is the haematogenous seeding of microbes into the vessel wall leading to vessel wall supuration and aneurysm formation [11].

Immunocompromised state results in susceptibility of patient susceptible to uncommon pathogens which are otherwise rarely to affect normal individuals [12]. Patients suffering from haematological malignancies especially when they are receiving chemotherapy are prone to fungal infections of lungs and sinuses. However fungal mycotic aneurysm in blood cancers has been reported rarely in literature. Zingale et al. reported case of T cell lymphoblastic leukemia in association with ruptured bacterial aneurysm of anterior communicating artery [13]. Minnerup et al.

Fig. 8 Repeat MRI brain after approximately 1½ year of initial presentation

reported a rapid aneurysmal development within 4 days in a case of CMML [14].

Susceptibility of aneurysm to rupture depends upon the size (average 11 mm vs. 5 mm) which in turn depends upon the immune status of the patient (larger size are more common with immunocompromised state) as reported in the Allen's series of cases [2].

Points to Remember

1. Cerebral mycotic aneurysmal rupture should be considered as one of the causes for intracerebral hemorrhage in a case of febrile neutropenia with pancytopenia.
2. Both invasive and non-invasive efforts should be made to find the etiology of intracerebral bleed.
3. Favorable outcome can be expected if mycotic aneurysm is detected and treated in timely manner.
4. Mycotic aneurysms secondary to fungal infections is a rare presentation.

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Compliance with Ethical Standards

Conflict of interest None of the authors have any conflict of interest to mention.

Ethical approval This article does not contain any studies with animals performed by any of the authors. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the participant included in the study.

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