BONE MARROW INVASION BY ASPERGILLUS SPECIE IN A SICKLE CELL TRAIT PATIENT WITH INVASIVE ASPERGILLOSIS: A FATAL CASE IN ASSOCIATION WITH DISSEMINATED INTRAVASCULAR COAGULATION

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ABSTRACT

Background: Invasive aspergillosis has been predominantly associated with pulmonary infection, particularly amongst immunocompromised individuals. Extrapulmonary infections with Aspergillus specie have been reported rarely irrespective of immune status. Risk factors for invasive aspergillosis include prolonged and severe neutropenia, haematopoietic stem cell and solid organ transplantation, advanced AIDS, and chronic granulomatous disease. The most frequently involved specie is Aspergillus fumigatus that constitutes over 90% of cases, followed by Aspergillus flavus, usually associated with a primary skin infection. Haematogenous spread to the bone causing osteomyelitis is the commonest form of disseminated aspergillosis and a surprisingly high proportion of these patients have no immunosuppression. We present a rare case of bone marrow invasion by Aspergillusspp. in a 3-year-old patient with sickle cell trait and chronic Aspergillosis. Case report: A 3-year-old patient with sickle cell trait was brought to the paediatric unit with recurrent diarrhoea, abdominal distention, weight loss and persistent cough. The child was severely wasted with generalised peripheral lymphadenopathy. She had marked respiratory distress and hepatosplenomegaly but no demonstrable ascites. Haematologic examination revealed leukaemoid reaction (leukocyte count of 44.0 x 10^9/L) with monocytosis (10%) and thrombocytopenia (platelet count of 97,000/mm^3); no blast cells were seen on blood film. The bone marrow was hypercellular with a myeloid/erythroid ratio of 20:1, consistent with infection. Bone Marrow culture yielded Aspergillus spp. and other results of sepsis work up were negative. Conclusion: Cases of extrapulmonary invasive aspergillosis have been reported rarely in both immunocompetent and immunocompromised patients. Haematogenous spread to the bone is the commonest form of disseminated disease.

Keywords: Bone marrow, Chronic, Invasive aspergillosis, Sickle cell trait.

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INTRODUCTION

Invasive Aspergillosis (IA) is an opportunistic fungal infection that is commoner in immunocompromised than immunocompetent individuals. It is acquired through inhalation of aerosolized spores. Invasive Aspergillosis is associated with higher morbidity and mortality in the setting of severe immunosuppression. Risk factors for IA include prolonged and severe

neutropenia, haematopoietic stem cell and solid organ transplantation, advanced AIDS, and chronic granulomatous disease. Infection with the fungus affects the respiratory tract in about 90% of cases.[1] Invasive aspergillosis most commonly involves the sino-pulmonary tract reflecting inhalation as the principal portal of entry. In the respiratory mucosa, inhaled spores germinate into hyphae, which invade the mucosa and lead to invasive pulmonary Aspergillosis (IPA).[2]

Over the approximately 185 different Aspergillus species identified, only a small percentage cause human disease.[3] The most frequently involved specie is A. fumigatus that constitutes over 90% of cases followed by A. flavus which usually cause primary skin infection.[4,5] Less-frequent causes include A.niger, A.terreus and A.ustus.[6,7] A study from the US reported that IA in children with compromised immunity was associated with prolonged hospital stay and increased total hospital charges compared with immunocompromised children without IA.[8]

Aspergillus species may colonise the skin to cause cutaneous infection and more rarely enter the body via the gut to cause gastrointestinal infection. Haematogenous dissemination is the commonest mode of spread to the bone causing osteomyelitis.[4] Other rarer sites of the disseminated disease include the central nervous system, cardiovascular system and other organs.[4,9] We hereby report a rare case of marrow invasion by aspergillus species in a 3-year-old patient with sickle cell trait and disseminated aspergillosis.

CASE REPORT

A 3-year-old girl was referred to the Specialist Paediatric Haemato-oncology unit from the general Paediatric outpatient clinic of the University of Maiduguri Teaching Hospital (UMTH) with 6 months history of recurrent diarrhoea, initially, blood-stained. The subsequent episodes were non-bloody, with a frequency of 4 to 5 times per day, each episode lasting 1 to 2 weeks and was diarrhoea free for 1 to 2 weeks, small in quantity, non-mucoid and no passage of worms. Three months after the onset of diarrhoea she was noticed to be progressively losing weight evident by the loosening of previously fitted clothes and appearance bony prominences. Two months before presentation she developed abdominal distension insidious in onset, progressively increasing but occasionally subsides following the passage of loose stool, there was associated abdominal pain which was poorly described that subsided 3 weeks before presentation. There was no vomiting, no yellowness of the eyes and no refusal to feed. One month later she developed a non-paroxysmal cough, non-barking and no associated difficulty in breathing. There was no history of established contact with adult having chronic cough, no history of ingestion of unpasteurised milk, she has had BCG vaccination with an evident scar. There was no history of fever. She had never been transfused. However, she has a sibling with sickle cell anaemia, but no history of sibling death or recurrent pregnancy loss of her mother. There was no family history of malignancy, no exposure to ionizing radiations, and no history of travels.

Physical examination revealed a child in respiratory distress with marked wasting. Vitals signs at presentation revealed an axillary temperature of 37.0^{0}C, respiratory rate of 50 cycles/min, pulse rate of 90 beats/min, blood pressure was 90/60mmHg, oxygen saturation at room air was 92%, and98% on oxygen via the intranasal route. The patient was pale with significant generalised peripheral lymphadenopathy, but not jaundiced, not dehydrated. The lymph nodes in the cervical region were firm, matted, non-tender, and no other features of acute inflammation with the largest measuring 1 X 0.5cm. However, no lymph node biopsy was done as caregiver effuse to give consent.There was no discharging sinuses and no pedal oedema. She weighed 10.5kg (75% of the expected for her age), height was 86cm (90.5%), mid-upper arm circumference (MUAC) of 11cm (severely malnourished).

She was in respiratory distress with widespread broncho-vesicular breath sounds, no adventitious sounds. The abdomen was grossly distended (abdominal girth: 69cm) with hepatomegaly of 10cm below the right sub-costal margin at the midclavicular line and a liver span of 14cm, the liver was smooth, firm, and non-tender. There was firm,

smooth and non-tender splenomegaly of 9cm. There was no demonstrable ascites and bowel sounds were normo-active. Examination of systems did not reveal any abnormalities.

Haematologic examination revealed a Haemoglobin concentration of 11g/dl, Total Leucocyte Count (TLC) of 44 x 10^9/L (Leukaemoid reaction) (normal range: 3 - 10 x 10^9/L), with neutrophils constituting 43%, lymphocytes 47%, and monocytes of 10%, and thrombocytopenia with a platelet count of 97,000/mm^3 (normal range: 100,000 - 450,000/mm^3). The blood film did not reveal any blasts. Bone marrow aspiration revealed hypercellularity with a myeloid/erythroid ratio of 20:1, erythropoiesis of mixed micro-normoblasts and megaloblasts. There was myeloid hyperplasia with sequential maturation consistent with infection of the marrow. Bone marrow culture yielded Aspergillus spp. However, cultures from blood and urine did not yield any growth while baseline tests for kidney and liver functions were essentially normal.

Chest Radiograph showed widespread nodular opacities with patchy shadows in both lung fields worse at the perihilar region and repeated chest radiograph after 2 weeks showed nodular opacities in the perihilar and basal regions which showed minimal resolution of the previously noted lesions (Figure 1). Abdominal ultrasound scan showed peri-porta, peripancreatic and para-aortic lymphadenopathy and also enlarged liver and spleen representing hepatosplenomegaly (Figure 2). Mantoux reaction was 0mm, early morning gastric washout for acid-fast bacilli was negative. Other baseline investigations that include liver and renal function tests, random blood glucose, and urinalysis were unremarkable. Human immunodeficiency virus (HIV) screening was negative.

A diagnosis of IPA with bone marrow involvement was made. She was commenced on IV voriconazole 6mg/kg q12hrly day 1, then 4mg/kg q12hrly for 6 days, then oral voriconazole at 4mg/kg q12hrly intended for 12 weeks. Four weeks later into the treatment with voriconazole the patient developed severe jaundice, upper GI bleeding and bleeding from puncture sites suggesting possiblevoriconazoleinduced liver injury and probable association of IA with disseminated intravascular coagulopathy (DIC). The bleeding was controlled following transfusion of fresh whole blood. A repeated LFT revealed derangement with a total bilirubin of 172µmol/L (normal: 1.7 – 17.1µmol/L), conj. bilirubin 131µmol/L (normal: 1.7 – 8.5µmol/L), total protein 63g/L (normal: 58 - 80g/L), albumin 29g/L (normal: 35 -50g/L), alkaline phosphatase activity of 221Iiu/L (normal: 60 – 170iu/L), ASAT of 24iu/L (normal: up to 15iu/L), and ALAT of 16Iiu/L (normal: up to 22iu/L). Voriconazole was stopped and Itraconazole intended to be introduced.

Five days later, she refused oral feeding and her caregivers declined nasogastric tube feeding. She developed hypoglycaemia (random blood glucose 2.0mmolL). A bolus of 10% dextrose at 200mg/kg was given and she was later maintained on 5% dextrose saline and oxygen therapy was also introduced when oxygen saturation in room air was 92%. Despite the initial improvement, her condition deteriorated. All efforts to resuscitate her failed and the patient died on day 42 of admission. The possible cause of death in our patient is possibly hepatic failure from voriconazole induced hepatocellular damage and disseminated intravascular coagulopathy.

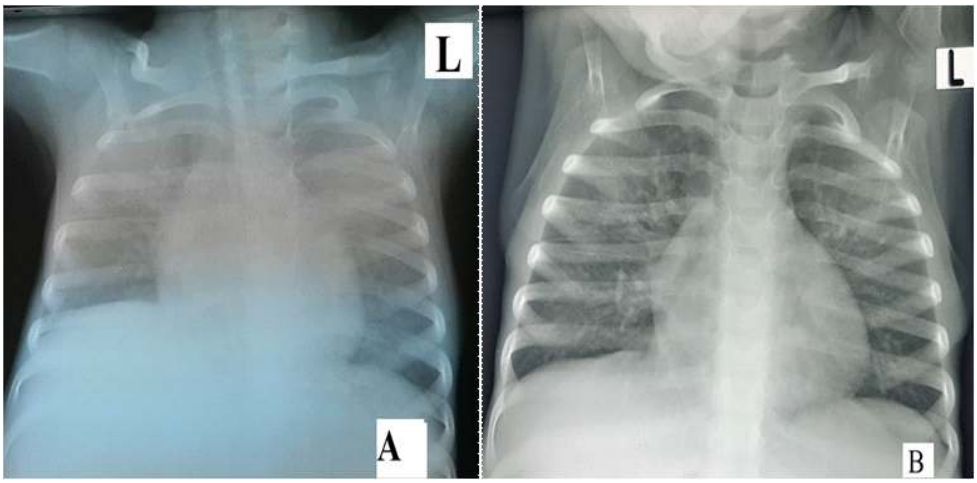

Figure 1:(A)Chest Radiograph showing widespread nodular opacities with patchy shadows in both lung fields worse at the perihilar region and (B) repeated chest radiograph after 2 weeks showing nodular opacities in the perihilar and basal regions.

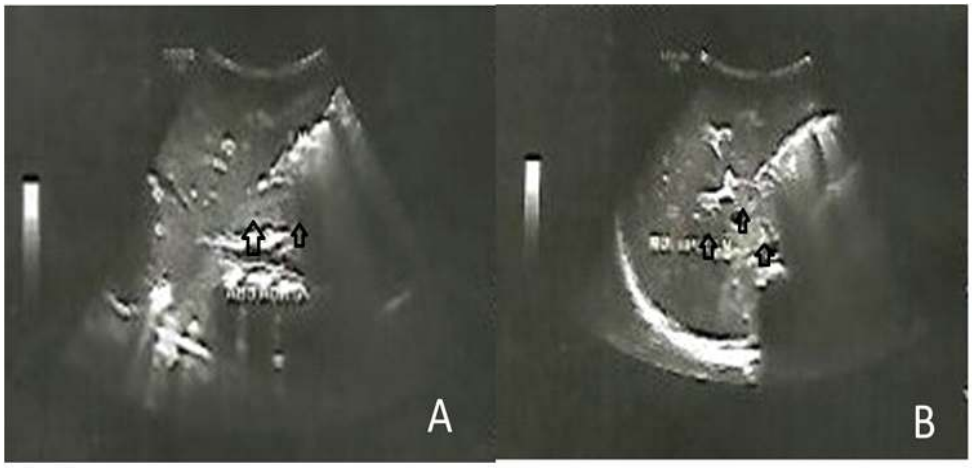

Figure 2: Ultrasound images (A & B) showing multiple peri-porta hepatic, and para-aortic regions lymphadenopathy as labelled with the black arrows.

DISCUSSION

Invasive Aspergillosis (IA) is a rare opportunistic disease seen in immunocompromised patients; it is extremely rare in immunocompetent patients and poses a serious diagnostic challenge.[10,11] Predisposing factors include leukaemia, use of steroids for chronic pulmonary diseases, other immunosuppressive drugs for the treatment malignancy, and other diseases such as diabetes mellitus, chronic granulomatous disease, or human immunodeficiency virus (HIV) infection all of which our patient did not have. The most common cause of human opportunistic fungal infection after Candida albicans is the Aspergillus species. The organism is in abundance in the environment, and common sources are decaying vegetation, stored grains, and soil.[5,6,7,10] Development of IA has been rarely described; mostly in adult Haemato-oncology settings.[12-14] The diagnosis of aspergillosis is often challenging because the symptoms are usually non-specific and overlap with those of pulmonary tuberculosis (PTB) and therefore most often delayed due to lack of clinical suspicion in patients without classic risk factors. Nigeria is ranked 6th among the 30 high TB burden countries in the world and 1st in Africa. Nigeria also accounts for 8% of the global gap between TB incidence and notified cases.[15] Nigeria contributes 9% to the global 3.6 million missing TB cases after India and Indonesia with 26% and 11% respectively. An estimated 418,000 new TB cases in Nigeria in 2018 and the country notified 104,904 (25%) and 106,533 cases of TB in 2017 and 2018 respectively giving a gap of 314,712 and 319,599 cases yet to be notified respectively.[16] This implies that a large number of TB cases are still undetected / missing thereby constituting a pool for continuous transmission of the disease in the community. The missing TB cases in Nigeria can be found among men, women and children with different forms of TB, including drug-resistant TB. The proportion of missing TB cases among children is more worrisome, as Nigeria was only able to notify 7% of the estimated childhood TB cases in 2017.[16]Withthe isolation of Aspergillus spp.

from the bone marrow, the diagnosis of IPA was highly possible; hence, a decision to treat with voriconazole, which is inconsistent with the recommendations from the 2016 updated clinical practice guidelines of the Infectious Diseases Society of America (IDSA).[17] In this situation where we had to use voriconazole, the serum level needed to be monitored;unfortunately, this is not available in our facility. Aspergillus infection in settings other than a haematopoietic stem cell and solid organ transplantation, prolonged and severe neutropenia, advanced AIDS, and chronic granulomatous disease, the patient may presents with symptoms progressing over several weeks to months, which was the case with our patient.[18-20] The acute form of invasive and disseminated aspergillosis is considerably more common than the chronic form and seen mainly in patients with diabetes mellitus, human immunodeficiency virus (HIV) infection or chronic granulomatous disease or those who have received corticosteroids for chronic obstructive air way disease; none of these was present in our patient. The usual symptoms of chronic aspergillosis in children are chronic cough, low-grade fever, weight loss and malaise for which the case reported presented with all. Even though, our patient did not have consistent clinical features suggestive of immunosuppression, the findings of massive hepatosplenomegaly, chronic cough and fever, led to her hospitalization and a work up for possible differential diagnoses. Unlike the invasive form, chronic aspergillosis occurs in immunocompetent patients.[11,21] Chronic pulmonary aspergillosis has also been reported to be the most subtle, yet severe long-term complication of chronic pulmonary infection than is generally appreciated.[22] There is considerable overlap in symptomatology between PTB and chronic pulmonary aspergillosis in children with chronic cough, fever, weight loss, fatigue and dyspnoea being common features.

The mortality rate of IA remains high, especially in resource-poor settings like ours and particularly in patients with DIC.[23] Presence of DIC in patients with IPA was associated with 93% death in Lai et al series,[23] and mortality rate exceed 50% in neutropenic patients,[24] and 90% in stem cell transplant recipients.[25]

CONCLUSION

Invasive aspergillosis and pulmonary tuberculosis can coexist in an immunocompetent child with considerable overlap in the clinical presentation of these chronic pulmonary infections hence the need for a high index of suspicion. Therapeutic approach should be evaluated case by case taking into account the likelihood of drug-drug interactions.

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