Disseminated Cryptococcosis Mimicking Miliary Tuberculosis with Generalized Lymphadenopathy in Immunocompetent Host

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Abstract
Cryptococcosis is a rare opportunistic infection in the immunocompromised host.1,2 Diagnosis of disseminated fungal infections is rarely thought of in immunocompetent hosts. In developing countries where tuberculosis is endemic, Cryptococcosis is often misdiagnosed as tuberculosis.3,4 A 14 year old girl, misdiagnosed as miliary tuberculosis with Koch’s abdomen on ATT, presented with seizures. After extensive workup, she was found to have disseminated Cryptococcosis, not tuberculosis. This case report shows the similarity in presentation of tuberculosis and Cryptococcosis, and hence Cryptococcosis should always be kept as a differential diagnosis of tuberculosis.

Introduction
Cryptococcosis, a rare disease of immunocompetent host but is common in the immunocompromised host. Human infection is mostly caused by Cryptococcus neoformans, which has two variants: C. neoformans var. neoformans (mainly reported in immunocompromised patients) and C. neoformans var. gattii (mainly reported in immunocompetent hosts). Cryptococcal infection can involve any part of body e.g. lungs, lymph nodes, brain/ meninges’, viscera, bone or skin or mucosa.2 Radiological presentation of pulmonary Cryptococcosis and miliary tuberculosis is somewhat similar and may lead to misdiagnosis.3–5 We are presenting the case of a 14 year old girl who was initially diagnosed as miliary tuberculosis with Koch’s abdomen. She had history of high grade fever with dry cough for 15 to 20 days and was started on ATT, initially responded to treatment but after one to two weeks patient again became febrile and came to our hospital and was diagnosed as disseminated Cryptococcosis.

Case Report
A 14 year old girl, diagnosed as a case of abdominal with miliary tuberculosis (sputum negative) on ATT Cat-I, presented with complaints of seizures (multiple episodes) in last six hours.

Patient’s father revealed that she had fever which was moderate to high grade, continuous, two to three spikes per day, associated with cough and mucoid expectoration since two months. Initially they had treatment from local practitioner but patient’s condition did not improve. She was then admitted in a government hospital on 18/5/15 and her investigations revealed anemia with marked leukocytosis, predominantly polymorphs, no hemoparasite seen. Liver and renal function tests were within normal limits. CRP positive and HIV, WIDAL and sputum for AFB – negative (Table 1).

Urinary routine and microscopy was within normal limit.

Her x-ray chest showed bilateral infiltrates in middle and lower zone (Figure 1).

CECT Chest showed centri-lobular nodules and reticulo-nodular densities in both lungs, multiple enlarged non-necrotic bilateral hilar, pretracheal, retrocaval, subcarinal, paraaortic, celiac, periportal, paraaortic, aortocaval and peripancreatic lymph nodes, few hypodense lesion showing mild enhancement within spleen, s/o infectious etiology like tuberculosis (Figure 2).

Sputum culture and sensitivity - E.Coli sensitive to netilmicin, imipenes, cefepime + tazobactam (treatment not instituted)

Patient was diagnosed as a case of sputum negative pulmonary and abdominal tuberculosis and Cat-I ATT was started under DOTS along with supportive treatment and patient symptomatically improved and discharged on 2/6/15.

Despite treatment, patient again became febrile one week after discharge. Fever was high grade and having two to three spikes per day associated with dry cough. Patient continued ATT. Nearly after one month of discharge patient developed multiple episodes of seizures.

On presentation to our hospital, patient was conscious but not oriented to time, place and person. Her vitals at the time of admission were Pulse – 110/min, BP – 120/80 mm Hg, SpO2 – 94%, febrile. On CNS examination, neck rigidity was present, Kernig’s sign negative, Left side Babinski sign positive, rest of systemic examination was within normal limits. Patient was suspected as a case of tubercular meningitis. Fundus examination was within normal limit.

Her investigations at our hospital revealed microcytic hypochromic anemia with marked Leukocytosis, predominantly neutrophils. No hemoparasite seen. Her renal and liver function tests were within normal limits (Table 1). Abdominal sonography revealed normal size liver with heterogenous echotexture, enlarged spleen along with normal pelvic study. HIV antibody test was negative. Blood culture and urine culture were sterile.

MRI brain showed subtle exaggerated meningeal enhancement with minimal prominence of the ventricles – suggestive of meningitis. Neurophysician reviewed the patient and asked for CSF routine and microscopy with ADA.

Patient’s lumbar puncture was done

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Table 1: Investigations

<table>
<thead>
<tr>
<th></th>
<th>Before Amphotericin B</th>
<th>After Amphotericin B</th>
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<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>8.6</td>
<td>7.2</td>
</tr>
<tr>
<td>TLC (cumm)</td>
<td>26000</td>
<td>16100</td>
</tr>
<tr>
<td>DLC (%)</td>
<td>92/05/02/01/00</td>
<td>74/18/06/02/00</td>
</tr>
<tr>
<td>Platelet (X10^3 cells/cumm)</td>
<td>2.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Serum Bilirubin (mg/dl)</td>
<td>0.7</td>
<td>1.95</td>
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<tr>
<td>Serum Proteins (g/dl)</td>
<td>6.7</td>
<td>5.67</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>SGOT (IU/ml)</td>
<td>74</td>
<td>97</td>
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<tr>
<td>SGPT (IU/ml)</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Alkaline Phosphatase (IU/ml)</td>
<td>158</td>
<td>441</td>
</tr>
<tr>
<td>Serum Sodium (mEq/L)</td>
<td>138</td>
<td>144.9</td>
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<tr>
<td>Serum Potassium (mEq/L)</td>
<td>3.2</td>
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<tr>
<td>RBS (mg/dl)</td>
<td>112</td>
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<tr>
<td>Blood Urea (mg/dl)</td>
<td>13</td>
<td>07</td>
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<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>0.72</td>
<td>0.22</td>
</tr>
</tbody>
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Abbreviations: TLC - Total leukocyte count; RBS - Random Blood sugar; HIV - Human immunodeficiency virus, Hb - Hemoglobin; Plt - Platelet count, S. Bil - Serum bilirubin, SGOT - Serum glutamate oxaloacetate transaminase, SGPT - Serum glutamate pyruvate transaminase, S Creat - Serum creatinine

which showed :- Appearance- clear, Coagulum - absent, Pandy’s - negative, Glucose - 58 , Proteins - 30, Total cells 110 (Polymorph – 15%, Lymphocytes – 85%), ADA - 03 U/L

As patient was already on ATT, repeat CECT chest and abdomen was done which revealed similar findings with no improvement. Chest physician's opinion was taken and advised higher antibiotics (i/v vancomycin) for suspicion of superadded bacterial infection.

Patient was planned for BAL and BAL done which revealed sterile reticulo nodular opacities, markedly decreased as compared to previous X-ray.

One day during morning rounds patient was re-examined and found to have sub-centimetric enlarged lymph nodes, in posterior triangle of neck, discrete, non-tender, freely mobile, largest measuring around 0.8 X 0.6 cm. Lymph node biopsy was done and histopathological examination revealed multiple Cryptococci in section (Figure 4). In view of lymph node biopsy findings, repeat CSF examination was sent for India ink preparation which revealed few capsulated budding yeast like organism suggestive of Cryptococcal meningitis.

Patient’s ANA profile was also done to rule out autoimmune disorder which came negative (ANA- negative, Anti-Sm-negative, SS-A – negative, SS-B – negative, Scl-70(DNA topoisomerase 1) – negative, Jo-1 – negative, dsDNA - negative).

On the basis of cervical lymph node biopsy, CSF examination and CT chest findings, a diagnosis of disseminated Cryptococcosis was made.

Patient was treated with injection Amphotericin B Deoxychalate 1 mg /kg body weight. After starting Amphotericin B patient developed
hypokalemia hence amphotericin b was stopped. After hypokalemia recovered, amphotericin b was re-instituted along with tab. Fluconazole 300 mg once daily. Patient responded to treatment and CSF was repeated after 2 weeks which showed no Cryptococci and chest X-ray after 6 months showed resolution in reticulonodular shadows (Figure 3).

CD4 count, complement levels and Immunoglobulin electrophoresis was normal.

Patient was discharged after 4 weeks of amphotericin B therapy on tab Fluconazole 300 mg once daily. Chest X-ray after 6 months showed marked improvement. CECT chest was done after 8 months of treatment which showed marked remission of disease. Patient is in remission at present.

Discussion

Cryptococcosis is caused by fungus Cryptococcus which multiplies extensively in bird faeces and they play an important role in multiplication of fungal colonies in soil. It is an ubiquitous yeast.6 Route of infection is pulmonary through inhalation of aerolized basidiospores. Infection of the lungs is mainly asymptomatic but it can lead to dissemination to the CNS, bones, kidneys, spleen, skin, adrenals and prostate.2,4-5 But disseminated Cryptococcosis almost always occurs in immunocompromised persons. We were not able to identify the source of infection in our case, but most probably infection is from soil or contaminated grains.

Symptoms mainly include fever, headache and malaise. Signs of meningitis are generally absent.2 Seizures may occur in CNS involvement. Skin lesions in disseminated Cryptococcosis are dome-shaped with central umbilation resembling molluscum contagiosum.

Diagnosis of cryptococcosis is made by detection of the yeast in biological fluids like CSF, or in histopathological specimens, stained with India ink. C. neoformans appears as narrow budding encapsulated yeast cells. Culture on concanavalin-glycine-thymol agar can be used to detect Cryptococcus by an antibody kit for serotyping or by DNA fingerprinting. A miliary pattern of infiltration is highly suggestive of miliary tuberculosis but also an unusual presentation of pulmonary Cryptococcosis.3,4 Philip et al. have described Cryptococcosis cases presenting with generalized lymphadenopathy with miliary mottling on chest X-ray.5 As in our case, patient was mistakenly diagnosed as a case of miliary tuberculosis with abdominal Koch’s on the basis of miliary shadows and hilar and abdominal lymphadenopathy on CT chest and abdomen.

Diagnosis of disseminated Cryptococcosis can be made by a positive blood culture or by a positive culture from minimum two different sites.7 In our case Cryptococcus was seen in CSF and in lymph node biopsy. Radiologically miliary shadows can also be found in Cryptococcosis which is also suggestive of pulmonary involvement (Figures 1, 2).

Cryptococcus neoformans has a variety of defense mechanisms to evade host immunity. Its intracellular location protects it from humoral immunity and decreases the efficacy of systemic antifungals.8 The polysaccharide capsule of Cryptococcus has anti-phagocytic action.

Conclusion

As clinical features and radiological findings of miliary tuberculosis and Cryptococcosis are somewhat similar so it is important to consider Cryptococcosis as a differential diagnosis if patient is not responding to anti-tubercular medications. Also, fungal infections are not being thought of in immunocompetent host. Thus, in patients showing relapse of symptoms or no response to therapy, fungal infection needs to be considered.

Acknowledgements

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References