Medical Mycology Case Reports 45 (2024) 100658

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Disseminated histoplasmosis: Long journey of a febrile young man

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ARTICLE INFO

Handling Editor: Dr Adilia Warris

Keywords:
Disseminated histoplasmosis
PUO
Fungus
Bangladesh
Histoplasma
PDH

ABSTRACT

A 19-year-old non-diabetic, non-HIV male presented with eighteen months of fever, weight loss, skin rash and lymphadenopathy. He was treated with anti-tubercular medication for more than twelve months in multiple institutions based on repeated biopsy reports of lymph nodes showing granuloma suggestive of tuberculosis. Before he was diagnosed at Bangabandhu Sheikh Mujib Medical University (BSMMU) with disseminated histoplasmosis at eighteen months of his disease, he already lost twenty kg weight, developed multiple small joint pain, back pain, and cough along with previously mentioned symptoms. Extensive investigations at BSMMU revealed biopsy material from multiple sites showed noncaseating granulomas with Periodic acid-Schiff (PAS) stain positive for budding oval yeast cells, and fungal culture revealed growth of dimorphic fungus suggestive of Histoplasma after three weeks. After treatment with intravenous liposomal amphotericin B with continuous itraconazole, the patient's fever completely subsided, his well-being improved, joint pain reduced, started to gain weight, and skin lesions started to heal. This case serves as a significant reminder that it is imperative to consider alternative diagnoses in patients who fail to show improvement with conventional antitubercular treatment.

1. Introduction

Histoplasma capsulatum, a dimorphic fungus, is the culprit organism responsible for disseminated histoplasmosis (DH), a relatively rare systemic fungal infection [1]. Birds and bats excreta contaminate the soil where this organism thrives, ultimately disruption of soil leads to this infection. Usually, infection occurs through high inoculum of microconidia inhaled through alveoli, via direct invasion, or in any person with a disrupted immune system [2]. Although asymptomatic lung infection is the usual scenario, individuals especially those with extremes of age, prolonged use of immunomodulators, and immunocompromised hosts e.g. diabetes, or acquired immunodeficiency syndrome [3]. It is believed to have a relatively higher incidence in tropical countries, in Bangladesh disseminated histoplasmosis is under-appreciated, where review articles showed fewer than thirty cases were reported [2].

Here, we present an eighteen-month-long and overwhelming journey of a febrile young male, who was repeatedly being treated for tuberculous lymphadenitis with poor response. Although the evidence around the diagnosis of tuberculosis (TB) was convincing enough for a TB-endemic country, other differentials of granulomatous febrile disease should be considered strongly when initial treatment fails. Keeping that in mind, we investigated the patient for both infectious and non-infectious causes of granulomatous disease and ultimately reached the confirmed diagnosis of disseminated histoplasmosis.

Therefore, we want to emphasize the significance of including disseminated fungal infections as a potential differential when managing cases of disseminated granulomatous infections in immunocompetent individuals, particularly in those from high TB prevalence areas.

2. Case summary

A 19-year-old non-diabetic, non-HIV male developed fever, and lymphadenopathy in different parts of the body and weight loss in December 2021. His illness started with high-grade, intermittent fever, accompanied by drenching night sweats. He noticed lymph glands swelling in the neck, armpits, and groins one month after the onset of the fever. Two months into his illness, he had profound anorexia and lost 5 kg of weight. The patient had contact with a known active tuberculosis (TB) patient who lived in the same household. He underwent a cervical

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https://doi.org/10.1016/j.mmcr.2024.100658
Received 26 June 2024; Received in revised form 2 July 2024; Accepted 4 July 2024
Available online 8 July 2024

lymph node biopsy that showed caseating granuloma suggestive of tuberculosis. Having a positive Mantoux test of 12 mm in 72 hours he was diagnosed as glandular TB and was prescribed six months of anti-tubercular medication. But he did not show any improvement after four months of therapy, at that time he was six months into his illness. So, another Fine Needle Aspiration Cytology (FNAC) was performed from a different cervical lymph node which revealed non-caseating granulomatous lymphadenitis. Assured of this finding, his physician advised him to continue his medication extending the regimen to eight months. However, there was still no improvement at the end of eight months of anti-tubercular therapy.

With ten months of fever and eight months of anti-tubercular medication, he was referred to a specialized tertiary care institute where he presented with ongoing fever, weight loss, lymphadenopathy, and new symptoms of non-inflammatory low back pain and joint pain in both hands. At the institute, his diagnosis of tuberculous lymphadenitis was re-confirmed based on repeating the cervical lymph node biopsy showing non-caseating granulomatous lesions suggestive of TB lymphadenitis. However, cervical lymph node aspirate material was also studied which showed negative for Mycobacterium tuberculosis (MTB) DNA, and Nontuberculous Mycobacteria (NTM) DNA on polymerase chain reaction PCR, and Xpert MTB/RIF assay. Mycobacterial culture of lymph node aspirate also showed no growth. The sputum test for acid-fast bacilli and Xpert MTB/RIF was negative. He was then prescribed a re-treatment schedule for tuberculous lymphadenitis that included a weight-adjusted fixed drug regimen for six months with levofloxacin and a tapering dose of prednisolone total for three months. His response to treatment improved while on steroids, with fever subsiding completely, lymph node size reducing, general well-being improving, and weight gain occured.

However, when he finished the three-month course of steroids, his condition deteriorated again despite being on his fifth month of re-treatment schedule, so he was referred to Bangabandhu Sheikh Mujib Medical University (BSMMU). At that point, he had history of eighteen months of fever, weight loss, and lymphadenopathy. Upon admission, he was febrile, moderately anaemic, emaciated with twenty kg weight loss, had multiple small joint pain in both hands with back pain, and cough (mostly dry). New skin changes appeared, with multiple papules, plaques with hemorrhagic crust, nodules, and lesions resembling molluscum contagiosum seen mostly over the face, neck, a few in the trunk, and limbs (Fig. 1). He also had generalized non-tender lymphadenopathy and hepatomegaly but no palpable spleen. He didn't give any history of intravenous drug abuse, blood transfusion, sexual promiscuity, recurrent oral or genital ulcer, travel history, or pet exposure.

Initial blood reports at BSMMU showed hemoglobin 9.0 gm/dl, red blood cell (RBC) 4.25x10^12/L, white blood cell (WBC) 1.87x10^9/L with neutrophil 80 %, platelets 22x10^9/L, reticulocyte count 0.07x10^9/L, peripheral blood film was consistent with pancytopenia, serum ferritin 353 ng/ml, transferrin saturation 6 %, lactate dehydrogenase (LDH) 273 U/L, bone marrow study showed micro normoblastic erythroid hyperplasia. Alanine aminotransferase 42U/l, aspartate aminotransferase 45 U/l, C-reactive protein (CRP) 63 mg/L, procalcitonin 0.6 μg/L. Other blood tests, including serum creatinine, serum electrolyte, serum cortisol, serum angiotensin-converting enzyme, serum calcium, urine routine study, Anti-nuclear antibody, rheumatoid factor, immunoglobulin (Ig)G, IgM, IgA, serum uric acid was normal, Interferon-Gamma Release Assays (IGRAs), anti-HIV (1 + 2) by enzyme-linked immunosorbent assay (ELISA), HBsAg, anti-HCV were also negative. Computed tomography (CT) scan of the chest with contrast was normal. Ultrasonography of the whole abdomen showed hepatomegaly (17.3 cm), splenomegaly (15 cm), and mild ascites. X-ray of the right hand showed multiple periarticular lytic lesions and magnetic resonance imaging (MRI) with contrast of lumber spine with the screening of spine showed spondylodiscitis of third lumber (L) vertebrae and pre- and para-vertebral resolving abscesses at L3-L4 level (Fig. 2).

We obtained three biopsy samples from bone marrow trephine, skin lesion of the neck, and bone biopsy from lumber third vertebrae. All three specimens showed multiple noncaseating granulomas, on the Periodic acid-Schiff (PAS) stain of all three specimens showed intracellular and extracellular small oval budding yeast cell morphologically consistent with Histoplasma species (Fig. 3). Finally, fungal culture revealed growth of dimorphic fungus suggestive of histoplasma plated on Sabouraud's dextrose agar after three weeks from tissue specimen obtained from skin biopsy which was incubated at room temperature.

The patient was diagnosed with disseminated histoplasmosis affecting the reticuloendothelial system as well as the skin, spine, and bones. The patient was started on injection of Liposomal amphotericin B (LAmB) for 14 days at a dose of 3mg/kg, followed by capsule Itraconazole 200mg, twice daily. After three weeks of treatment patient's fever completely subsided, well-being improved, joint pain reduced, started to gain weight, and skin lesions started to heal (Fig. 1, Table 1). Initial treatment with itraconazole will be continued for a period of one year, after which the patient will be re-evaluated. At this point, the patient is in the tenth month of treatment, while his disease is under remission.

3. Discussion

Disseminated histoplasmosis is rarely reported in Bangladesh where the first reported case of histoplasmosis was in 1982 and the second one was in 2005. Although, Bangladesh is thought to be an endemic risk zone for histoplasmosis, a handful number of cases were reported. One possible explanation might be due to the underlying great mimicking granulomatous disease 'tuberculosis' [4].Although disseminated histoplasmosis is a disease of immunocompromised patients, it has been reported previously in immunocompetent individuals like in our patient [5]. HIV is a strong risk factor for DH, while Bangladesh has the lowest amount of HIV only 0.01 %, unlike Latin America where histoplasmosis prevalence is higher 2–20 % due to the higher amount of people living with HIV/AIDS [6,7].Our patient had no obvious risk factors, no possible exposure to any avian excreta, and neither didn't have any recent injury from where the organism can enter directly. Although new research is showing individual genetic variation and makeup may predispose to an apparently immunocompetent individual susceptible to invasive fungal diseases [8].

Our patient presented with pyrexia, weight loss, and night sweats. Among systemic findings he had lymphadenopathy, hepatosplenomegaly, spine involvement, and rheumatological features, but no pulmonary involvement, which is thought to be a major feature in DH [9]. Although skin lesions are more common in immunocompromised persons, immunocompetent patients like ours can present papules, nodules, plaques, crusts, mucosal ulcers, and erosions [10]. In an endemic tuberculosis zone, a patient with prolonged pyrexia, weight loss, and lymphadenopathy, almost always physician expects tuberculosis. When backed by histopathology reports of caseating granuloma, usually there remains no doubt about the possibility of TB, even if, in many cases, acid-fast staining of samples or mycobacterial culture comes with negatives. In our patient, physicians continued more than one year of anti-tubercular treatment, even when the patient had little to no response, the most likely cause was repeated positive granulomatous lesions of the biopsy materials. Eventually, our patient responded well to

Table 1
Comparing patient's treatment response to LAmB after 21 days of therapy.

Lab parameter	Before LAmB	After LAmB
Hb	7.4 gm/dl	10.2 gm/dl
RBC	3.51x10^12/L	4.4x10^12/L
ESR	80 mm in 1st hour	35 mm in 1st hour
WBC	2x10^9/L	3.3x10^9/L
Neutrophil	67 %	56 %
Platelets	18x10^9/L	110x10^9/L
CRP	91 mg/L	8 mg/L

Fig. 1. Before and after changes in appearances and skin lesions of LAmB therapy.

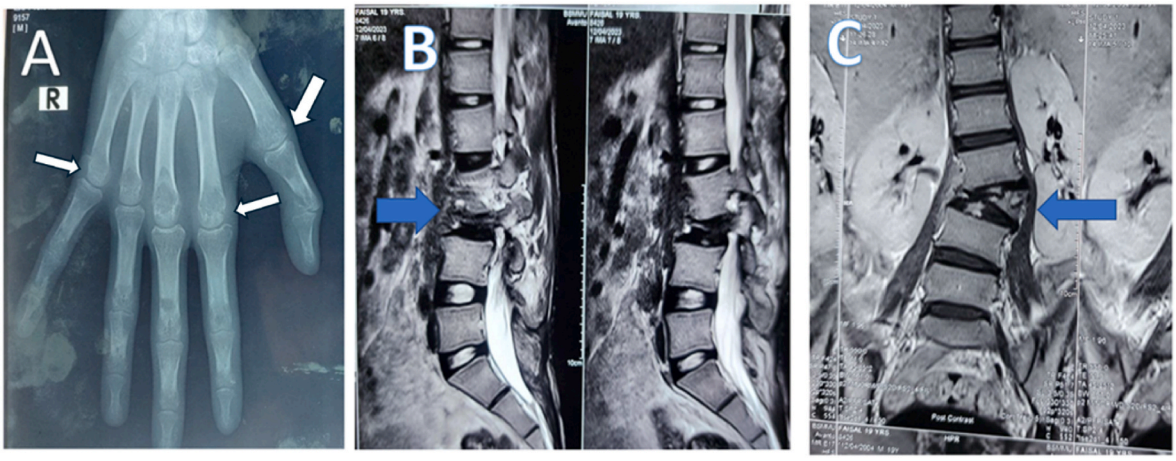

Fig. 2. A) lytic lesions in X-ray hand (arrows), (B) and (C) pre- and para-vertebral soft tissue abscesses with disc involvement.

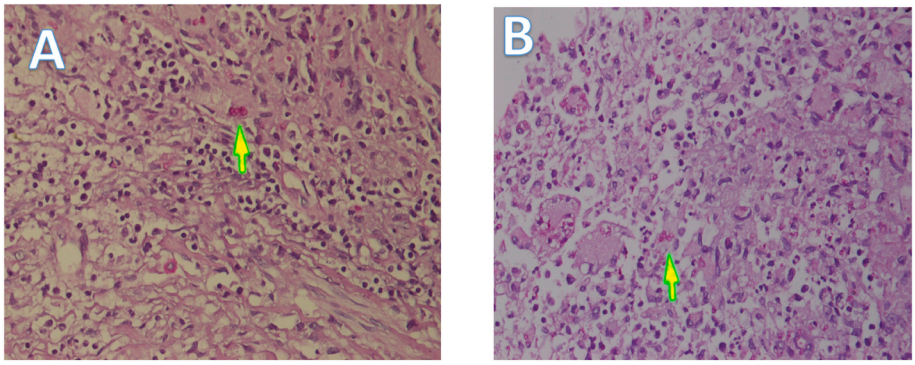

Fig. 3. (A) Bone marrow trephine biopsy (B) skin biopsy; both showed noncaseating granulomas intracellular and extracellular small oval budding yeast cell.

the conventional treatment regimen of liposomal amphotericin B followed by oral itraconazole [11].

4. Conclusion

This case serves as a significant reminder that it is imperative to consider alternative diagnoses in patients who fail to show improvement with conventional treatments. Despite initial signs pointing towards tuberculosis, the lack of response to anti-tubercular therapy warranted further investigation, ultimately leading to the diagnosis of disseminated histoplasmosis. A comprehensive evaluation of differentials in such unusual cases might limit the suffering and possibly lower the mortality.

Disclosure

Authors have no funding source.

Informed consent

Informed consent was taken from the patient.

Ethical approval

Not applicable.

CRediT authorship contribution statement

Sudip Kumar Banik: Investigation. **Chowdhury Adnan Sami:** Writing – review & editing, Conceptualization. **Md Mizanur Rahman Khan:** Investigation, Conceptualization. **Shohael Mahmud Arafat:** Supervision, Project administration. **Abed Hussain Khan:** Supervision.

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