Unabridged Histoplasmosis Myositis: Unsolved Dissemination with Diagnostic Challenge

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Abstract
Histoplasmosis occurs predominantly in immunocompromised hosts and typically presents with mild constitutional symptoms, weight loss, weakness, fatigability, hepatosplenomegaly, and lymphadenopathy. The diagnosis is generally delayed and is based upon isolating the organism in blood cultures or by identifying intracellular organisms in tissues. Disseminated Histoplasmosis is well described in HIV patients but Histoplasmosis myositis is a rare manifestation and has not been reported in seronegative patients till date. We here address a case of a pharmacologically immunosuppressed patient with extensive Histoplasmosis myositis invading almost all the skeletal muscles of body (including plantar foot muscles) with no evidence of dissemination to other organ-systems. Clinical examination and investigations co-related with infiltrative muscle disease and skeletal muscle biopsy revealed Histoplasma capsulatum. This patient illustrates a distinctive clinical presentation of fungal infection with subtle constitutional symptoms and isolated muscle weakness which added to the diagnostic challenge. Hence, differential diagnosis of fungal infection must always be considered as a cause of myopathy in any pharmacologically immunosuppressed patient.

Keywords: Fungal infection, histoplasmosis, muscle disease, PET/CT, pharmacological immunosuppression

Introduction
Histoplasmosis is usually asymptomatic but pneumonitis or dissemination may occur. Disseminated histoplasmosis is usually seen among immunocompromised individuals, including those with AIDS, hematologic malignancies, and post solid organ transplant. Commonly, the source of infection is via inhalation of the dimorphic fungal microconidia into the lungs. An extensive and isolated Histoplasmosis myositis is a very rare manifestation though well described in HIV patients but is not reported in seronegative patient till date. We hereby report a unique case of extensive infective myositis due to Histoplasma capsulatum with history of bronchial asthma on intermittent steroids.

Case History
A 65-year-old gentleman was admitted to the hospital with intermittent fever since two months, loss of appetite and weight loss (4 kg over 2 months). He also complained of increasing weakness and pain in lower limbs with difficulty in walking. He was a known asthmatic for last 15 years. For seasonal aggravation of asthmatic symptoms, he used intravenous hydrocortisone (100 mg/day) with inhaler Salbutamol (200–400 mcg/day) on alternate days for 2–3 months every year. For the last one year he was also on some indigenous treatment (ayurvedic medicine), of unknown nature as powder formulation along with intermittent supplementation with intravenous hydrocortisone 100 mg for occasional worsening of symptoms.

On examination, he was hemodynamically stable but febrile (101°F). General physical examination revealed features of steroid overdose. On neurological examination, mental status, and cranial nerves were normal with generalized muscle tenderness and muscle power of 3/5 (MRC) in lower limbs, 4/5 in upper limbs, and 5/5 in distal muscles. Sensory examination and deep tendon reflexes were normal. Blood biochemistry and microbiology were unrevealing of infective etiology and are depicted in Table 1. Serum procalcitonin and CD4 cell counts were also within normal range. Blood serology for bacterial, fungal and viral agents (HIV, HBV, HCV) were negative. Sputum examination for nocardia, AFB, and vasculitis work up including ANA and ANCA were negative. Contrast Computerized tomography of chest and abdomen, Magnetic resonance imaging of the brain and bone marrow biopsy also did not show any abnormality.

In view of proximal weakness nerve conduction study (NCV) and electromyography (EMG) was planned which revealed myopathic pattern with spontaneous activity (fibrillation and positive sharp waves) supporting infiltrative myopathy.

Positron Emission Tomography (PET) was performed to search for unexplained constitutional symptoms including...
fever and weight loss. The PET scan revealed granulomatous lesions suggesting the probability of inflammatory/infective myopathy [Figure 1] Muscle biopsy from frozen and paraffin section of left vastus revealed inflammatory cells supporting infective etiology and presence of yeast form of fungus (morphology consistent with *Histoplasma*) within skeletal muscle bundles confirming Histoplasmosis myositis [Figure 2].

With the histological confirmation of the diagnosis, treatment was started in the form of intravenous Amphotericin B deoxycholate 50 mg/day (0.8 mg/kg) for 3 weeks with regular monitoring of renal functions.

He was discharged after 4 weeks on oral Itraconazole 200 mg twice a day for 6 months and inhaler salbutamol and budesonide for asthma. On last follow up, after 2 months of discharge he was afebrile, asthma was well controlled and with no muscular pain or weakness.

**DISCUSSION**

Infection with *Histoplasma capsulatum* occurs commonly in endemic areas but is symptomatic in those with defects in cellular immunity only. The spectrum of infection includes chronic, slowly progressive infection to acute, severe, life-threatening sepsis in immunocompromised patients. Histoplasmosis predominantly present in immunocompromised hosts with mild constitutional symptoms including weight loss, weakness, fatigability, hepatosplenomegaly and lymphadenopathy.[2] Immunosuppressed conditions, either due to corticosteroids or HIV infection, manifesting atypically as fasciitis and myositis and requiring medical care has very rarely been reported.[3] In immune-competent hosts, muscle and connective tissue are generally not invaded by fungi except direct extension from a focal infection.[4] We report an isolated *Histoplasma* invading the axial and appendicular muscles with no evidence of dissemination to other body organs as blood culture, sputum analysis, and bone marrow examination were negative for fungal growth.

Our patient illustrates a distinctive clinical presentation of infection with symptoms as fever, weight loss, and isolated muscle weakness which added to the diagnostic challenge. The normal levels of muscle enzyme, Creatinine phosphokinase (CPK) in this case may be related to low muscle mass and immunosuppression therapy but clinical history and electrodiagnostic findings were consistent with diagnosis of active myopathy. Nuclear study of the whole body guided the diagnosis when the clinical and conventional imaging work-up were negative in identifying the etiology of symptoms.[5] The key clue to diagnosis was obtained from nerve conduction study (NCV) and electromyography (EMG) examination suggesting infiltrative myopathy. Muscle biopsy was the necessary next step to elucidate the cause which revealed the presence of yeast form of fungus consistent with Histoplasma endorsing the infective etiology.

The pre-existing pharmacological immunosuppression probably predisposed the patient to muscle invasion by *Histoplasma* which was responsible for these signs and symptoms though muscle enzymes were normal.

Amphotericin B was prescribed as it is known to cause rapid clearance of fungal burden.[6] Clinical improvement with increase in muscle strength and resolution of myalgias was noted after the two weeks of antifungal therapy suggesting that histoplasmosis was the cause of the active myopathy According to literature, itraconazole is theazole of choice following initial amphotericin B treatment for mild to moderate Histoplasmosis. Hence, it was prescribed for six months seeing the extensive nature of the disease.

The extent and involvement of almost all skeletal muscles of the body (including plantar foot muscles) by the fungus

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**Table 1: Laboratory investigations**

| Investigation                  | 16/8/2019 | 25/8/2019 | 14/9/2019 |
|-------------------------------|-----------|-----------|-----------|
| Haemoglobin                   | 11.9 gm/dl| 10.7 gm/dl| 11.2 gm/dl|
| Total Leucocyte count         | 9.0 X10^3 mm\(^3\) | 10.2 X10^3 mm\(^3\) | 8.9 X10^3 mm\(^3\) |
| Differential Leucocyte count  | 84.5%/10.4%| 85.7%/10.1%| 85.8%/9.4%|
| Platelet count                | 337 X10^3/µl | 328 X10^3/µl | 341 X10^3/µl |
| ESR                           | 26 mm     |           |           |
| LDH                           | 239 U/L   |           | 97 U/L    |
| Cratinine phosphokinase (CPK) | 187 U/L   | 131 U/L   | 56 U/L    |
| Blood sugar                   | 80 mg/dl  |           |           |
| Liver function tests Bil/SGOT/SGPT/Alk. phosphate | 0.9/54/52/32 | 0.0.8/48/50/38 | |
| Blood urea/sr. creatinine     | 42/0.9    | 38/1.1    | 40/0.8    |
| Sodium/Potassium/Magnesium (mmol/L) | 129/4.5/1.7 | 135/3.8/1.9 | 133/4.0/1.2 |
| 1-3 beta D glucan            | 35.6 pg/ml|           |           |
| Brucella antigen              | Negative  |           |           |
| Elisa for Scrub typhus        | Negative  |           |           |
| Thyroid Function Tests (T3/T4/TSH) | 2.73/18.09/0.315 |          |           |
| ANA/ANCA                      | Negative  |           |           |
| Urine routine and culture     | Normal    |           |           |
without dissemination to other body organs still remains a clinical mystery.

**Key Messages**

Conclusively, the lessons learnt from this case include: -

- Consider fungal infection in differential diagnosis of myopathy in any pharmacologically immunosuppressed patient

**What is known**

Histoplasmosis is common in patients who are immunocompromised, especially HIV infection but there is no evidence in literature of histoplasmosis presenting as isolated muscle infection.

**What is new**

Extensive isolated fungal myositis in a pharmacologically immunosuppressed patient with no evidence of dissemination to other organs has not been reported earlier. Positron Emission Tomography (PET) imaging showing extensive involvement of Histoplasma in all the muscles of the body including the axial muscles is unreported.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.
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