CASE REPORT

Disseminated Histoplasmosis in a Non-Immunocompromised Child

M Hasliza, MBBS (Mal)*, N A Nur Atiqah, MRCP (Paed), C B Lim, MRCP (Paed), I H M I Hussain, FRCP, Institute of Paediatrics, Hospital Kuala Lumpur, 50586 Jalan Pahang, Kuala Lumpur

Summary

We describe a 2 year-old non-immunocompromised girl with disseminated histoplasmosis who presented with a 2-month history of fever and bloody diarrhoea. On presentation, she was severely wasted and anaemic. There were gross hepatosplenomegaly and multiple lymphadenopathy. A septic screen was negative. A subsequent stool culture isolated *Salmonella enteriditis*. Serial Widal-Weil Felix (WWF) titres showed serological response after 2 weeks of Ceftriaxone. However, she continued to have spiking fever, bloody diarrhoea and weight loss. She developed pancytopaenia and disseminated intravascular coagulation. A bone marrow aspirate and trephine, and lymph node biopsy showed the presence of *Histoplasma capsulatum*, confirmed by Gomori-Methenamine Silver staining. She responded to intravenous amphotericin B followed by fluconazole (intravenous then oral) for 6 months after discharge. Human Immunodeficiency Virus screening tests were negative. Complement and immunoglobulin levels were normal. T and B enumeration tests showed gross leucopaenia with very low T cell function with defective phagocytic function. A repeat T and B cell enumeration test and phagocytic function tests done 3 months later were normal.

Key Words: Disseminated, Histoplasmosis, Non-immunocompromised, Child.

Introduction

Disseminated Histoplasmosis is not uncommon in South East Asia though this region is not known to be a major endemic area for this organism[1]. It is however known to occur among immunodeficient patients in non-endemic areas either from reactivation of the latent form of infection or from exogenous exposure to microfoci located within the non-endemic regions[2]. Such cases have been reported among Human Immunodeficiency Virus (HIV) infected patients[3,4] and diabetics.

Over the years, more cases have been reported from this part of the world, suggesting that histoplasmosis may have been underdiagnosed or present subclinically[1]. We describe a case of Disseminated Histoplasmosis in a 2 year-old non-immunocompromised girl from Kuala Terengganu.

Case Report

The patient was a 2 year-old Malay girl from a non-consanguineous marriage; her father is a poultry farmer. She presented with a 2-month history of fever and bloody diarrhoea. She had hepatosplenomegaly and lymphadenopathy (submandibular, jugulodigastric, postauricular, axillary, inguinal) which were firm in consistency and varying from 2 to 3cm in diameter. The cardiovascular and nervous examination were normal. Initial investigations showed anaemia (Hb 8.2 g/l), total white count 8 400 /ul with a normal differential count and ESR of 22 mm/h. Full blood picture showed

response to infection and chest X-ray showed pneumonic changes. Septic workup done initially in the local hospital i.e. blood, urine, stool cultures, bone marrow aspirate and trephine biopsy and culture, Widal-Weil Felix (WWF) test, screening tests for tuberculosis, malaria, collagen disorders and Human Immunodeficiency Virus (HIV) were negative. She was treated with intravenous ampicillin and gentamicin, then cefotaxime and finally ceftriaxone, with no improvement. She was then referred to Hospital Kuala Lumpur.

On examination her weight was very much below the 3rd centile for her age. She had a liver of 4cm palpable below the right costal margin and a spleen of 3cm.

A stool culture isolated *Salmonella enteritidis*. A repeat WWF test showed an elevated titre of T (O) 800 and T (h) 1600. After 2 weeks of ceftriaxone, WWF titres were 200 and 800 respectively. However, she continued to have spiking fever, bloody diarrhoea and weight loss. She developed pancytopaenia and disseminated intravascular coagulation. HIV antibody detection by particle agglutination and ELISA were again negative. Antigen detection by polymerase chain reaction was also negative. Complement and immunoglobulin levels were normal. However, T and B cell enumeration tests showed gross leucopaenia with very low B and CD4 T-lymphocyte counts were low. There was borderline low T cell function with defective phagocytic function. A repeat bone marrow aspirate, trephine and culture and lymph node biopsy were performed. An intracytoplasmic organism was seen in the bone marrow aspirate (Figure 1 and 2), trephine roll and the lymph node tissue. Gomori-methenamine silver staining confirmed the presence of *Histoplasma capsulatum* (Figure 2). She was treated with intravenous Amphotericin B, with a starting dose of 0.1mg/kg/day, gradually increasing to a maximum of 2mg/kg/day, for a total of 63 days. (Total cumulative dose of 92mg/kg.) Fever settled on day 53 of therapy. She was supported with total parenteral nutrition (TPN) throughout her illness. Intravenous fluconazole 4mg/kg was added from day 49 of amphotericin B and continued for 6 months after discharge. Although itraconazole is the drug of choice for oral maintainence therapy for Histoplasmosis, fluconazole was used instead because *Toluropsis glabrata* (sensitive to fluconazole) was isolated from the TPN line.

Prior to discharge to Kuala Terengganu Hospital, the patient remained afebrile for a week, her appetite

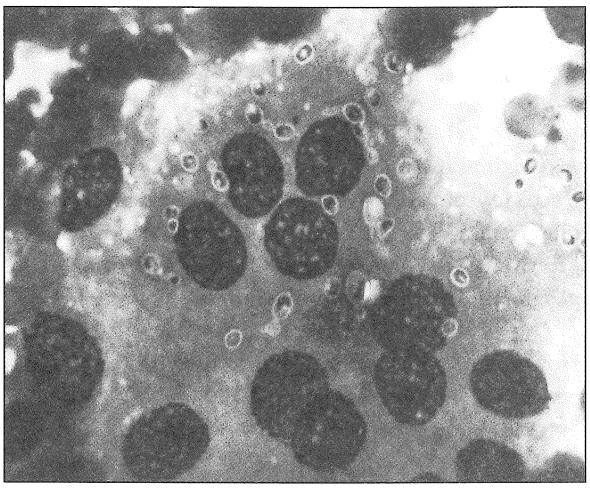

Fig. 1: Bone marrow aspirate showing presence of an intracytoplasmic organism which is Histoplasmosis capsulatum.

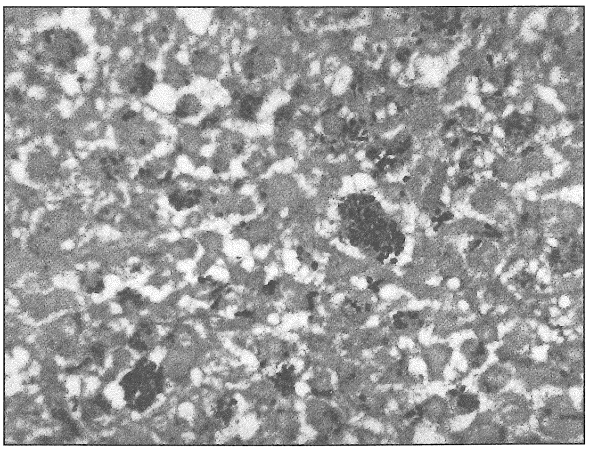

Fig. 2: Bone marrow aspirate showing presence of Histoplasma capsulatum (Gomori-methenamine Silver staining)

improved tremendously and she also gained weight. As the immune function tests were done during the acute phase of the illness and may be a consequence of the overwhelming infection, a repeat T and B cell enumeration and phagocytic function tests were performed when she had fully recovered from the illness. These tests were confirmed to be normal.

Discussion

Histoplasmosis is an opportunistic, inhalation-acquired systemic mycosis, caused by a dimorphic mould, *Histoplasma capsulatum*[5]. Infectious particles are found in soils mixed with bird or bat faeces such as chicken coups, bird roosts and places frequented by bats. Our patient's father is a poultry farmer.

The primary infection occurs by the respiratory route, with lesions in the lungs that are usually mild and self-limited. The clinical spectrum of progressive disseminated histoplasmosis (PDH) is broad - from a chronic form with non-specific constitutional symptoms such as fever, cough and malaise, to the fulminant, acute form which may resemble septic shock with a high fatality rate. The midspectrum of subacute PDH tends to pursue a more relentless course with death within 2-24 hours if not treated. Both the chronic progressive cavitating form and dissemination can also occur and may be fatal[6]. The estimated incidence of PDH is approximately 1 per 2000 cases of histoplasmosis in normal adults. Acute PDH and disseminated disease with multiorgan invasion is rare in immunologically normal individuals, except after a heavy inoculum. However, it is considerably higher among infants, very young children, in Hodgkin's disease and in immunocompromised adults, especially HIV patients.

Nearly all acute PDH among infants and children appear to be an extension of the primary infection in which pulmonary signs and symptoms are prominent. If not treated, this could progress to gastrointestinal bleeding, disseminated intravascular coagulopathy, granulocytopaenia with associated sepsis as common terminal events.

Definitive diagnosis of Histoplasmosis require growth of fungus from samples of body fluid or tissue e.g. sputum, bronchoscopic aspirate, blood or bone marrow culture and cerebrospinal fluid culture. The yield is much lower in chronic PDH compared to in acute PDH. This yeast can also be visualised from sections of biopsies from infected tissues when stained with haematoxylin and eosin, Gomori silver methenamine procedure and the Wright-Giemsa method. In this case, the Histoplasma was seen in the marrow and lymph node biopsy.

The yeast form of *Histoplasma* can be confused with the cyst forms of *Pneumocystis carinii* which are larger, extracellular and do not bud. Intracellular amastigotes of *Leishmania* species and trophozoites of *Toxoplasma* gondii may resemble yeast forms, but neither take up fungal silver stains[5]. Serologic tests for complement fixing antibodies and immunoprecipitating antibodies are adjuncts to the diagnosis of Histoplasmosis because of the difficulty in detecting the organism by culture or staining methods or skin testing in several forms of the disease[3]. Nevertheless, there is no correlation between the level of antibody and severity of illness, particularly in immunocompromised patients.

Solid-phase radioimmunoassay (RIA) can detect *Histoplasma* antigen in urine and serum, and is thus useful in the immunocompromised patient with suspected disseminated Histoplasmosis which may not be detected from the serology tests[7]. The specificity of the technique is high although false positive reactions have been observed in patients with *Blastomyces dermatitidis* and *Coccidiodes immitis*.

Approximately 90% individuals develop skin test reactivity to histoplasmin after a primary infection and most retain reactivity for many years. Hence, it is of great value for epidemiological studies and for mapping geographic distribution of the fungus.

However, it is useless for diagnosis because a substantial percentage of the population living in endemic areas become skin test positive by the age of 18-20 years.

Neutrophils may play a significant initial role in limiting infection but it is the CD4 T-lymphocytes which are crucial to host defence against *H. Capsulatum*[7] and the CD8 T-lymphocytes which are necessary for

optimal clearance of the organism. In our patient, the CD4 counts were low during the acute infection. This may explain her fulminant course.

Amphotericin B continues to be the drug of choice for life-threatening disease although the introduction of azole compounds into clinical practice have broadened the treatment options of Histoplasmosis[8]. Amphotericin B is highly effective in chronic and subacute forms of PDH in the absence of endocarditis and central nervous system infection. A total of 35mg/kg is recommended and relapse is infrequent after a full course. In our patient, we continued with amphotericin B beyond this recommendation because the fever only settled on day 53 of treatment.

Ketoconazole is an acceptable drug used in the non-immunocompromised with chronic and subacute PDH with a dosage of 400mg/day for 6-12 months. Alternatively, itraconazole 200mg b.d. may be given orally for maintainence therapy. It is also interesting to note that our patient initially also had salmonellosis. This could be explained by the fact that diffuse parasitisation of the reticuloendothelial system (RES) by *Histoplasma* organisms may cause 'RES blockade' which then predisposes to systemic salmonellosis[9].

Conclusion

Disseminated histoplasmosis can rarely occur in the non-immunocompromised. We reported a previously healthy child presenting with gastrointestinal symptoms, signs of hepatosplenomegaly, generalised lymphadenopathy and failure to thrive who survived a stormy clinical course of disseminated intravascular coagulation with associated fungal septicaemia.

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