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Case Report

Brucellosis as a Cause of Febrile Neutropenia in Acute Myeloid Leukemia: A Case Report

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Abstract: Brucellosis is an important zoonosis predominantly afflicting animal and dairy product handlers. Its occurrence as a hospital acquired infection especially in febrile neutropenia has been reported only rarely. We present a case of acute myeloid leukemia that developed febrile neutropenia during the course of induction chemotherapy when blood culture grew brucella. He responded to appropriate anti-microbial therapy, attained complete remission and was subsequently taken up for further chemotherapy.
Keywords: Brucellosis, Febrile Neutropenia, Myeloid Leukemia

INTRODUCTION

Brucellosis also called Undulant fever, Mediterranean fever, Malta fever, is usually caused by close contact with dairy animals or consumption of their unpasteurized products. Brucella are small, non-motile, non-spore bearing, gram negative, aerobic, intracellular coccobacilli linked to disease in animals. Humans are usually infected in the setting of occupational exposure to animals or animal products. Consequently most affected patients are either animal handlers or involved in the dairy products business. Transmission from human to human either by sexual contact, blood transfusion or mother to child transmission has also been reported rarely [1, 2]. The clinical spectrum of brucellosis involves acute, sub-acute and chronic infections. Acute brucellosis resembles a viral illness with fever, myalgias, arthralgias, night sweats and may be complicated by orchitis, meningo-encephalitis or infective endocarditis. Chronic brucellosis is primarily a disease of joints with spondylitis, sacroiliitis and peripheral arthritis. Sequel of disease may be orchitis, uveitis, meningitis and granulomatous hepatitis. Haematological abnormalities may occurs especially in acute brucellosis and include anaemia, thrombocytopenia and leucopenia. Hematological abnormalities are generally self-limiting with successful treatment. Out of all the Brucella species, B mellitensis is most commonly reported as a human pathogen.The majority of reports of brucellosis come from endemic regions and the majority of patients have some history of contact with cattle or sheep.

CASE REPORT

The patient was a 55 year old male admitted with history of fever, generalised weakness and gum bleeding of 2 weeks duration. Clinical examination revealed pallor, gum hypertrophy and firm, non-tender, discreet left cervical nodes of 2 cm diameter. Peripheral smear, bone marrow morphology, cytochemistry and immunophenotyping were consistent with AML – M5a. Bone marrow cytogenetics revealed monosomy 7 in 16 out of 20 metaphases. He was managed with 3+7 induction regimen (daunorubicin 45 mg/m^2 and cytarabine 100 mg/m^2) along with supportive measures. On Day+11 he developed high grade fever (104.2 °F) with chills and rigors. Blood cultures from the central line and peripheral veins grew a pure growth of Brucella mellitensis. Blood culture was performed using BacT/ ALERT 3D 60 (bioMerieu, Inc) and isolate identified by VITEK2 compact (bioMerieu, Inc) systems. The antibiogram was performed using Kirby-Bauer Disk Diffusion Susceptibility Test Protocol and revealed sensitivity to imipenem and piperacillin-tazobactam, resistance to cefotaxime, ceftazidime, ceftriaxone, trimethoprim-sulphamethoxazole, streptomycin, gentamicin, and amikacin. Haemoglobin was 8.3 gm/dl, total leucocyte count was 750 /mm3, absolute neutrophil count was 67 /mm3. The patient was on ciprofloxacin prophylaxis at the time. Blood culture by conventional means grew the same organism. Brucella serology was strongly positive with a 2-mercaptoethanol titre of 1:640 and an agglutination titre of 1:5120. He was managed with piperacillin-tazobactam 4.5 gm q 8h and doxycycline 100 mg q 12h.

The patient became afebrile by Day +17 after 5 days of antimicrobials. Total leucocyte count at the time was 1330/mm3, ANC 13/MM3. Blood culture was sterile. Piperacillin-tazobactam was continued for 10 days and doxycycline for 14 days. Blasts disappeared from peripheral blood on Day +15. The patients' blood counts began to recover by Day +23 and he attained complete remission on Day +30. He was then taken up for second cycle of chemotherapy.

During the second cycle of induction chemotherapy - ADE regimen) he again developed febrile neutropenia when blood culture grew Klebsiella and he responded to appropriate antibiotics. After 8 weeks of treatment agglutination test and blood culture for Brucella were both negative. The patient was then taken up for subsequent cycles of chemotherapy.

DISCUSSION

The etiology of febrile neutropenia can be variable with a large spectrum of gram positive and gram negative organisms being isolated in centres across the world. The majority of infections reported are gram positive cocci although in recent years the trend has shifted towards gram negative bacilli. The picture has changed in various centres as a result of different antimicrobial prophylaxis protocols.

The various species of brucella have been linked to specific animal carriers. B mellitensis affects goats and sheep, B abortus afflicts cattle, B suis causes swine brucellosis, B canai affects dogs. B mellitensis though primarily a pathogen of sheep and goats has also been isolated from cattle [3].

Certain geographical areas over the world are endemic for brucellosis such as the Middle East, Mediterranean Europe and Africa, Central America, Central Asia and India [4,5]. Most of the infections occur in sheep handlers, abattoir and dairy industry workers and veterinarians. Other than this the most common sources of infection are soft cheeses, yoghurt and ice-creams prepared from unpasteurized milk. A large epidemiological survey of brucellosis in an endemic region found that the majority of cases had a history of animal contact (86 %) with or without consumption of unpasteurized dairy products (68 %). Only in 1 % of cases was the infection ascribed to other causes [4]. Our patient did not give a history of animal contact but hails from a region with high reported rates of brucella seropositivity [6]. Also, one of the staple dishes of this region is a kind of unprocessed cheese called 'kalari' which may have been a source of infection.

Brucellosis related to febrile neutropenia has been reported in acute leukemia, solid tumour chemotherapy, bone marrow transplantation. However, almost all these case reports originate from the Middle East which is a known endemic region for brucellosis [7-11]. To the best of our knowledge this the first case report from India; we could not find any similar reports in literature from this region.

The recommended treatment -gold standard- of brucellosis is a combination of intramuscular streptomycin and oral doxycycline for a minimum of 6 weeks [11, 12]. Other anti-microbial agents commonly used for the treatment of brucellosis are trimethoprim-sulphamethoxazole, ciprofloxacin,gentamicin and rifampicin [5,13]. Vaccine treatment was used in Eastern European countries initially without documented efficacy [4]. Ciprofloxacin has been used for the treatment of brucellosis including as a first line drug in febrile neutropenia in acute leukemia and bone marrow transplant [11, 14]. This patient developed brucellosis while on ciprofloxacin which is the standard antibacterial prophylaxis at our institution. Moreover, his antibiotic sensitivity test revealed resistance to, not only ciprofloxacin, but also the aminoglycosides (streptomycin, gentamicin and amikacin) and trimethoprim-sulphamethoxazole. Finally he responded to a 2 week course of piperacillin-tazobactam and doxycycline with clinical improvement. Thereafter, the patient underwent subsequent cycles of induction therapy without recurrence of brucellosis. Blood culture and agglutination test performed at 8 weeks did not suggest any reactivation of infection.

Brucella being a slow growing organism can lead to delay in diagnosis and appropriate treatment in febrile neutropenia even where a high index of suspicion exists. In this case of acute myeloid leukemia with no history of contact with animals, we had no reason to consider brucella in the etiology of febrile neutropenia. In this case we were fortunate to have access to an automated system which gave early results as well as a precise bacteriological diagnosis in 6 hours. This gave us time to institute antibiotics and meanwhile confirm the results using conventional culture plates and serology as well as perform antibiotic sensitivity tests.

CONCLUSION

We have discussed a rare case of brucella related febrile neutropenia in a case of AML with no history of animal contact. The antibiotic sensitivity test revealed resistance to most first line agents for brucellosis, however the patient responded to a short course of synthetic penicillin and tetracycline.

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