Case study

Brucella Bacteremia in a Patient with Metastatic Carcinoma Stomach in a Tertiary Oncology Centre; Case Report and Review of Literature.

Abstract:

Identification of commonly encountered pathogens and their comprehensive understanding has become the utmost requirement for oncologists to treat the disease. (1) Human brucellosis is one of them. This is class B bioterrorist agent and one of the highly neglected tropical diseases which is clinically under diagnosed, underreported because its diagnostics issues, and also it's property to masquerade various other infectious and non infectious conditions. Here is the unique and first case report from India which presents brucella bacteremia in a solid cancer patient. In spite of all care and treatment patient succumbed to death.

Key word: Brucella melitensis; Stomach Cancer; Chemotherapy; Bacteremia

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Background:

Though major advances in the cancer care have resulted in improved survival of patients over the past several decades, yet infections remain a significant cause of mortality. The main risk factors for infections in cancer patients are uncontrolled malignancy, immunosuppressive and cytotoxic chemotherapy, thus making them more susceptible to a wide range of opportunistic bacterial infections. Therefore, identification of commonly encountered pathogens and their

comprehensive understanding has become the utmost requirement for oncologists to treat the disease. (1)

Human brucellosis is a class B bioterrorist agent and commonest bacterial zoonosis quite prevalent in the developing countries. This is one of the highly neglected tropical diseases which is clinically under diagnosed, underreported because its diagnostics issues, and also its' property to masquerade various other infectious and non infectious conditions. Therefore, the exact burden of this problem is not known in India, especially in cancer patients. (2) It is well known that patients with cancer may present with atypical symptoms of brucellosis owing to their abnormal cellular and humoral immunity, neutrophil dysfunction and oncologists must be aware of its potential effects in the cancer management. In countries like India, brucellosis must be considered in the differential diagnosis of febrile neutropenia in the patients with cancer and rapid, sensitive and automated diagnostic platforms are required to make early diagnosis and proper management in patients. (3). Moreover, there are hardly any studies in India, which have specifically, find the epidemiology of brucella infection in cancer patient. Here is the unique and first case report from India which presents brucella bacteremia in a solid cancer patient.

Case Report:

A 54-year-old gentleman, known case of metastatic carcinoma stomach came to the Medical oncology OPD at Tata Memorial Hospital (TMH) Varanasi in February 2022 with complaints of persistent low back pain radiated to bilateral lower limb from7-8 months back. On Positron emission tomography (PET) scan, metastasis was found in the right iliac bone. In view of advanced malignancy, he was planned for palliative chemotherapy in the form of injection docetaxel 80 mg , injection oxaliplatin 120 mg, injection 5-Flourouracil 1950 mg regimen in a

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total 4 cycles to be given every two weeks along with monthly zoledronate 4 mg injection. Post 4 cycles, the patient had partial response, however, grade II peripheral neuropathy, thus, oxaliplatin was discontinued. Post 8 cycles, the patient had maintained partial response and the patient was planned for docetaxel maintenance chemotherapy 3 weekly. During the course of chemotherapy, the patient suffered from the increased pain in lower back which was radiating to the left leg. Bilateral Contrast-Tomography Doppler was done to check the metastasis and it was suggestive of lytic sclerotic lesion involving the right inferior iliac spine only. Due to persistent backache, the patient was given palliative radiotherapy with 8 Gy, one fraction. In spite of all treatment, patient appeared acutely ill over due course of therapy, developed fever and altered sensorium. The patient was admitted for supportive care. Physical examination revealed pallor, no external lymphadenopathy or palpable abdominal organomegaly, and normal cardiovascular systems. At the time of admission, patient was having raised temperature of 102^0F and not oriented to time, place, and person. Following 24 hours to empirical antibiotics (Cefoperazone–Sulbactum and levofloxacin), the fever responded but clinical condition deteriorated. Urine routine examination showed acidic pH, Blood (3+), specific gravity 1.020, protein 2+, ketone negative, urobilinogen negative, nitrate negative. Microscopic examination showed 2-4 pus cells/HPF, 40-50 RBC/HPF. Complete blood examination showed the following results: high white-blood-cell-count of 13,830/mm3 (neutrophils: 94.10%, lymphocyte: 3.5%, Monocyte: 1.8%, and Eosinophil: 0%), hemoglobin level of 11.20 g/dl, platelet count of 287000/ml, hyponatremia (127.2mmol/l), CRP of 0.9 mg/dl, creatinine level of 1.78 mg/dl and albumin level of 1.9 g/dl, alkaline phosphatase: 128mg/dl. Paired sets of blood cultures (Bact-alert bottles) were obtained in microbiology laboratory. Blood cultures were performed with the BacT/Alert blood culture automated system. (Biomeriux- Franc-Germany). The patient's relatives refused

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for further treatment and took the patient home. Palliative care consult was taken for home care program. On telephonic follow-up, the patient succumbed to death one day after discharge.

The automated blood culture system flashed positive after 72 hours of incubation. Gram-stain of broth showed Gram negative-coccobacilli. Positive blood cultures were sub-cultured onto 5% sheep blood agar, chocolate agar, and mac-conkey agar plates which were incubated at 35°C. After 24 hour of incubation, white creamy pinpoint colony grown in blood agar (>10^5 cfu/ml) while Mac-conkey agar have significant growth (>10^5 cfu/ml) of tiny non lactose fermenting colonies. Further identification was done using an automated VITEK-MS system version 9.01 (BioMerieux, France) using N-280-Gram-negative-cards. The blood cultures grew: *B. melitensis* sensitive to ciprofloxacin (<0.25), amikacin (<0.20), gentamicin (<1.0) and minocycline.

Discussion:

Brucellosis is the commonest anthropozoonotic infection with a pandemic distribution and remains an uncontrolled problem in regions of high endemicity such as Mediterranean, Middle East, Africa, Latin America and parts of Asia. It is caused by the facultative gram negative bacteria belonging to the genus Brucella. Human infection can occur through consumption of unpasteurized dairy products and raw meat or through skin abrasions. Brucellosis detected after the diagnosis of malignancies reveals high mortality in cancer patients which requires the need for more meticulous care in managing such infections in cancer patients. To the best of our knowledge, clinical summary of only 9 cases of brucella infection in cancer patients is published in the literature, since 2000 to 2022 (Table 1). The incidence of brucella infection in cancer patients is scarce from India. To our best of knowledge, this is the first case report of brucella

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bacteremia in a patient with metastatic brain malignancy. Out of 9 published cases only one case was reported in India in AML patient in 2014. Published literature of 9 cases represents data of predominantly male patients with a mean age of years (range, 6–77 years). Interestingly, Most of them had a hematological malignancy (77%) and only 23% patients had solid tumors. Underlying given table-1 is summarizing the clinical features and outcome of brucella infection in cancer patients. Most of the published cases are reported mainly from Turkey (Southeastern Europe). Most of the cases are belong to rural area and are in close contact of pet and animals. Total of 78% cases were associated with hematological cancer and 22% were with solid tumors. Overall mortality was present in 44.44% cases died in duration of course of therapy. All cases presented fever, 4 cases present with joint pain, weakness, fatigue and two with bleeding manifestations. In 6 cases blood and bone marrow culture were positive the bacteremia. Our case is remarkable because it represents the first reported case of brucella melintensis bacterimia associated with solid malignancy in India.

Although, there is no direct link with the Brucella bacterimia and the advanced stage of carcinoma of stomach in the patient however this type of opportunistic infection progresses rapidly to the mortality of the cancer patients if ignored in developing countries like India. Also the origin of infection could not be traced because patient expired after one day of discharge from hospital and at that time blood culture did not flashed positive due to slow growth of brucella like organism. But consumption of unpasteurised milk could be one of the important risk factor for the infection of brucella in this patient. Therefore case reported shows that paying special attention to opportunistic infections and endemic diseases in cancer patients receiving chemotherapy regimens may reduce mortality. In majority of patients, Brucellosis was detected after cancer diagnosis and the prevalence of the patients who died when cancer and brucellosis

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were concurrently diagnosed is 37.5%. Therefore such opportunistic infections must be considered as one of the differential diagnoses. Because if not treated immediately this may lead to high mortality of the immunocompromised patients.

Though India is endemic for brucellosis, further studies are required to know the true incidence in the cancer population. Also, there is urgent need to develop rapid, reliable, highly sensitive and easy to perform automated blood culture systems to detect brucella species because conventional culture media are reliable enough to detect and takes long time to grow the bacteria (minimum 14 days) (2) Routine serological testing for brucellosis in patients with prolonged febrile illness can help but these are not much reliable in cancer patients. The slow growth of Brucella in blood cultures and the late-emerging manifestations of Brucellosis prevent the disease from being diagnosed at the early stages infection and may cause the treatment failure of empiric antibiotics (4)In many cancer patients, abroad spectrum antibiotics like aminoglycosides, anti-pseudomonal beta-lactam prescribed following the onset of fever can partially affect isolation of bacteria.(4) Further studies are recommended to be conducted on diagnosing this opportunistic pathogen prevalence in cancer patients. In this case report, clinical symptoms were bewildered to predict the sepsis therefore it should be noted that only cultures are the test that proves bacteraemia for these cases.

In conclusion, accurate managing and treatment of underlying opportunistic infectious diseases such as brucella bacterimia is essential in improving cancer patient prognosis. Cancer patients may present with atypical symptoms of brucellosis, which is a rare condition even in endemic countries, and clinicians should be aware of its potential effects in the cancer treatment.

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References

1. Christopher S, Umapathy BL, Ravikumar KL. Brucellosis: review on the recent trends in pathogenicity and laboratory diagnosis. *J Lab Physicians*. 2010;2(2):55-60

2. Darazam I, Imanzade F RabieiMM Shokouhi S Erdem S Brucellosis in Patients with Neoplasm; A Research Article, I: https://doi.org/10.21203/rs.3.rs-191086/ 2021

3. Dogu MH, Nizam N, Eren R, Suyani E. Is it Brucellosis or Multiple Myeloma? Or can it be both? Journal of Hematology. 2016;1(1):3.

4. Payandeh M, Amirifard N, Sadeghi M, Sadeghi E. Rectal Cancer in Patient with Chronic Lymphocytic Leukemia Association with Brucellosis: The First Case Report. 2016.

5. Tyagi A, Verma T, Agarwal S, Gupta RM. Brucellosis as a Cause of Febrile Neutropenia in Acute Myeloid Leukemia: A Case Report. :3.

6. Akkoyunlu ME, Akkoyunlu Y, Hakyemez IN, Erboy F, Arvas G, Aslan T. Lung cancer, brucellosis and tuberculosis: remarkable togetherness. Asian Pac J Trop Dis. 2013 Aug;3(4):327–30.

7. Caglar Citak E, Arman D. Brucella Melitensis: A Rare Cause of Febrile Neutropenia. Pediatric Hematology and Oncology. 2011 Jan 20;28(1):83–5.

8. Al-Anazi KA, Al-Jasser AM. Brucella bacteremia in patients with acute leukemia: a case series. J Med Case Rep. 2007 Nov 23;1:144.

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Year	Location	Age/sex	Occupation	Symptoms	Treatment	Cancer	Test	Outcome

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9. Emara DMM, Vyas DV, Essam DT. Synchronous Occurrence of Brucellosis and Ovarian Cancer- A Case Report. :4.

10. Eser B, Altuntas F, Soyuer I, Er O, Canoz O, Coskun HS, et al. Acute Lymphoblastic Leukemia Associated with Brucellosis in Two Patients with Fever and Pancytopenia. Yonsei Med J. 2006 Oct 31;47(5):741–4.

Table 1: Clinical features of Brucella cases (2000-2022)

2016(3)	Turkey	72/M	NA	Joint-pain and fever	Tetracycline & Rifampicin	Brucellosis with Multiple Myeloma	Rose-Bengal plate test	Alive
2015(4)	Iran	77/M	NA	Weakness and fatigue	Cotrimoxazole + Rifampicin	Rectal Cancer in Patient with Chronic Lymphocytic Leukemia	Bone marrow aspiration	Alive
2014(5)	India	55/M	NA	fever, generalized weakness and gum bleeding	Piperacillin/tazobactam 4.5 gm Doxycycline 100 mg	Febrile Neutropenia in Acute Myeloid Leukemia	Blood cultures	Alive
2013(6)	Turkey	68/M	Farmer	Expectorating sputum, Intermittant fever, night sweats,	Streptomycin 1 g/d, Rifampin 600 mg/d doxycyclin 200 mg/d	Lung cancer tuberculosis	Blood cultures	Recovered & alive
2011(7)	Turkey	6/M	Rural habitant Contact	Fever	Trimethoprim-sulfamethoxazole&rifampin	Myelodysplastic Syndrome Presenting as	Rose bengal agglutin	Recovered &

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			with pet dog			Pancytopenia and Fever of Unknown Origin	ation	alive
2007 (8) 2007 (8), (9)	Saudi Arabia Kuwait	57/M 54/M 48/F	NA NA House maid	chronic relapsing brucellosis for 15 years fever, pain and abdominal	Rofloxacin 500 mg twice daily continued on oral doxycycline Doxycycline 200 mg twice daily for 3 weeks,	Brucella bacteremia in patients with acute leukemia Synchronous Occurrence of Brucellosis and Ovarian Cancer	blood cultures Blood cultures NA	Died

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					streptomycin 1gm im OD, tablet rifampicin 600 mg o.d and Doxycycline 100 mg			
2006 (10)	Turkey	39/F 40/F		weakness, headache, nausea, vomiting and fever fever, weakness, headache and weight loss	(streptomycin 1g/day/intramuscularly, doxycycline 100 mg	Acute Lymphoblastic Leukemia Associated with Brucellosis in Two Patients with Fever and Pancytopenia	bone marrow culture blood and bone marrow cultures	

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