Case study

A opportunistic bacterimic infection by *Nocardia farcinica* in patient with advanced brain cancer in at an oncology centre in North India

Abstract

Nocardia farcinica is an emerging opportunistic pathogen in immunocompromised patients.A case of fatal N. Farcinica bacteremia in a 52-year-old man with brain cancer is described. He was admitted with complaints of fever, forgetfulness along with increased aggressiveness and occasional fits. N. farcinica was isolated from blood cultures obtained at hospital admission and was identified by automated system. Patient could not survive and succumbed to death after 48 hrs of antibiotic treatment. Early identification and antibiotic susceptibility testing is are necessary for nocardiosis is highly important because of its the highly-resistant antibiotic profile and to improve the chances of survival.

Introduction:

Nocardiosis is a rare opportunistic disease that primarily affects patients with deficient immune system. *N. farcinica,* the pathogen of bovine farcy, is one of the rare species of Nocardia and it represents less than 3% of all Nocardia cases. This is being increasingly recognized as a cause of human infection, particularly in immunocompromised patients. Nocardia is an aerobic gram-positive rod bacterium that belongs to the Actinomycetes genus and is primarily distributed in the soil. Nocardia was first described by Nocard in 1888 as a fungus but was later classified as an aerobic bacterium and member of the genus Nocardia.(1) The patients with advanced malignancy or undergoing chemotherapy are already in immunocompromised condition and are more susceptible for acquiring the oppurtunsitic opportunistic infections like Nocardia. The cancer patients residing in endemic rural areas and or living under unhygienic conditions are more prone to getting infection by opportunistic infections pathogens, leading to adverse complications and fatal outcomes in those patients.

Case Report:

A 52-year-old diabetic man on oral hypoglycemic drugs was admitted to the Tata Memorial Cancer Center, Varanasi (MPMMCC) with complaints of forgetfulness, headache and nausea for past 15 days. About 3 months ago he was had been diagnosed with high grade brain tumor at TMH Mumbai, for which he underwent right parietal craniotomy and biopsy of splenial (corpus callosum) tumour and was planned for therapeutic radiation. Patient was referred from Tata Memorial Hospital/Mumbai to a local radiotherapy centre at native place but due to aggressiveness of patient radiation treatment could not be done. The histopathology of tissue was suggestive of high grade infiltrating glial tumour of astrocytic morphology.Patient was has been continuing levetiracetam 500mg twice daily along with intermittent steroids since his surgery. He was planned for a fresh Contrast Enhanced MRI of brain followed by focal, conformal external beam radiation therapy with concurrent Temozolomide (TMZ) in our centre. For radiation treatment, simulation was done and planned for CEMRI brain. But due to disease progression and associated symptoms, MRI brain could not be done. He developed Covid on 18.01.2022 and defaulted for further treatment. He presented 3 weeks after with drowsiness, low grade fever, increased aggressiveness, occasional fits and progressive dyspnoea for which he was admitted for supportive care. On admission, he appeared acutely ill. The physical examination revealed a temperature of 38.4°C, respirations 40 per minute; blood pressure, 90/60 mm Hg, and pulses 130 per minute. Laboratory data showed the following results: a white blood cell count of 13,870/mm3 (neutrophils: 90.1%, lymphocyte: 1.8%, monocyte: 4.8%, and eosinophil: 0.1%), hemoglobin level of 15 g/dL, platelet count of 162,000/mL, NT Pro BNB BNP 48pg/ml, blood urea 45.7 mg/L, creatinine level of 0.51mg/dL and albumin level of 3.0 g/dL total protein, 5.5 g/dL. Paired sets of blood cultures were obtained, and he was started on empirical intravenous antibiotics (Cefaperazone-sulbactum, 1g tid; levofloxacin, 500 mg bid). During the following 24 hoursIn next 24 hours, the patient condition deteriorated further with his own illness despite palliative care but further admission in hospital was refused by his relatives. Twenty-four hours later after his discharge patient succumbed to death. The aerobic blood cultures yielded a Gram-positive branching rod. Blood cultures were performed with the BacT/Alert blood culture automated system. Positive blood cultures were subcultured onto 5% sheep blood, chocolate agar, and Sabouraud dextrose agar plates, which were incubated at 35°C. Antimicrobial susceptibility was determined using the standard Broth microdilution method following the recommendations of the Clinical and Laboratory Standards Institute (CLSI, 24th edition).

Antibiotics were selected according to the first-line and second-line drugs used for *Nocardia* recommended in CLSI M24-2A, including amikacin (AMK), linezolid (LNZ), trimethoprim/sulfamethoxazole (TMP-SMX), ceftriaxone (CRO), ceftazidime (CAZ), cefepime (CPM), imipenem (IPM), tobramycin (TOB), ciprofloxacin (CIP), amoxicillin-clavulanic acid (AMC), and minocycline (MIN). The antibiotic susceptibility was judged as susceptible, intermediate, or resistant based on the breakpoints recommended in CLSI M24-2A. *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were used as controls. Antimicrobial susceptibility testing using the disk diffusion method, showed susceptibility to ciprofloxacin (40mm), amoxicillin/clavulanic acid(25mm), minocycline(25mm), linezolid(40mm), tigecycline (24mm) and amikacin (35mm), but resistance to ertapenam(26mm),piperacillin/tazobactam(21mm),ceftriaxone(20mm),cefotaxime(25mm),cotrimoxazole(6mm),cefepime(10mm),meropenem(14mm),cefazolin(6mm),ceftazidime(6mm), gentamicin(16mm). Initial presumptive identification was performed according to the colony morphology on solid medium, Gram stain appearance, acid-fast staining and modified acid-fast staining, following the standard protocol. Grey white colonies on culture plates, branching Gram-positive bacilli, positive acid-fast staining and positive partial acid-fast staining were identified as *Nocardia* species. *Nocardia* species were further verified by MS identification using an automated VITEK-MS system (BioMerieux, France) as *Nocardia Farcinia.*

Discussion:

We describe a case of fatal N. Farcinica bacteremia in a patient with advanced brain cancer, and review the literature on Nocardia infections in cancer patients. Nocardiosis is an ancient disease that remains a public health problem in many impoverished locations worldwide. Nocardia is an aerobic gram-positive rod bacterium that belongs to the Actinomycetes genus and which is primarily saprophytic soil microorganism.Nocardia infection produces a life-threatening infection in patients with defective cell-mediated immunity. There are multiple risk factors that predispose patients to infection with Nocardia, and conditions or medications that suppress cell-mediated immunity predominate. Since infection occurs by inhalation of contaminated dust and by traumatic implantation of the actinomycete, the lungs and the subcutaneous tissues are the usual sites of primary nocardiosis. The organism can subsequently invade other sites by hematogenous dissemination and infective foci can develop in distant organs. Disseminated

disease is potentially life-threatening, and usually follows a primary lung infection. The frequency of disseminated disease has been reported to range between 28% and 56%. Although it is believed that dissemination and metastatic infective foci are due to bloodstream spread, the isolation of N. farcinica from blood cultures is rare. Repetitive Because of its controversial status, N. farcinica was not described as a cause of human nocardiosis in the literature for some years. Since its characterization as a distinct species, cases of N. farcinica infection are increasingly reported: This is the first infection which is due to *N. farcinica* reported from India in cancer patient. Bacteremia due to Nocardia infection occurs as opportunistic diseaseoccurring mainly in patients deficient in T cell-mediated immunity. Patients with the greatest susceptibility to this infectioninclude those with solid organ transplant and hematopoietic stem cell transplant recipients, HIV-infected patients and patients taking corticosteroids chronically. Nocardia Genus It contains more than 219 species that have been described till date with the rapid increase growth in number of cases caused by it the genus Nocardia, The most commonly encountered species are Nocardia brasiliensis, Nocardia cyriacigeorgica, Nocardia farcinica, and Nocardia nova. Nocardia steroides is the most frequently found species causing noncutaneous invasive disease. Once Nocardia spreads to the central nervous system, the mortality is 100%. Specific risk factors were found in 94% of patients. To the best of our knowledge, a clinical summary of only 10 cases of Nocardia infections in cancer patients have been published in the literature from 2004 to 2021 (Table 1). Nocardia incidence studies in cancer patients are scarce from India.

To our best of knowledge, this is the first case report of Nocardia farcinica in Brain cancer patient. Nocardia farcinica is one of the less? least common species among the various species. Although blood cultures rarely show positive results, the bacteria may disseminate from the primary site of infection. Herein, we describe an immunosuppressed patient diagnosed with disseminated nocardiosis caused by Nocardia farcinica.The published literature of 10 cases represents data of predominantly patients with a mean age of 65.4 years (52-67 years).Interestingly, Most of them had a solid tumor with 60% cases of Lung cancer, 20% colon cancer, 10% case of brain tumor &and rest ofmultiple myeloma. Most of the cases presented withcough, fever, vomiting and weight loss. Our case is remarkable because it represents the first reported case of Nocardia infection associated with Brain tumor in a male patient.

Nocardia species were was isolated from the blood culture in the present case in eastern India. Nocardia farcinica was initially identified on the basis of microscopy, antibiotic sensitivity pattern and biochemical reaction susceptibility pattern and finally identified on automated system.In most of the reported cases, the preliminary identification was Nocardia spp. and the exact identification was only performed later. Because of its specific multiresistant antibiotic pattern, the identification of N. farcinica have to be done as soon as possible as it isessential to guide the selection of appropriate antibiotics by the for clinicians.Because of its highly resistant antibiotic profile, early N. farcinica identification and antibiotic susceptibility testing are necessary to improve the chances of survival.Treatment would be advised in cancer and immunocompromised patients with increased risks of developing septicemia.

This study describes a fatal case of an advanced brain malignancy who was immune-compromised due to the ongoing chemotherapy. This patient presented with a feature of febrile neutropenia, vomiting, forgetfulness along with increased aggressiveness and occasional fits.Treatment of this underlying infection required to stophold the chemotherapy for good time and to adapt patient-specific cancer treatment according to the balance between both need of cancer control and infection treatment according to the susceptibility test as in our case. But due to advanced nature of malignancy and palliative stage intent of cancer treatment, patients relative denied for the further admission of patient in the hospital and asked for the lama (leave against the medical advice).

Conclusion:

This is the first Nocardia infection casein patients from remote poor areas in North India. Thus patients with malignancy are more prone to acquire infection fromsoil and water transmission.Therefore, early detection in the laboratory and essential safety measures for preventing soil and water transmission infections is the key to avoiding fatal outcomes and adverse complications of in an immunocompromised cancer patient.

Based on our case and recent reports of nocardiosis, there may be a role for close clinical monitoring in patients with severe neutropenia for opportunistic nocardiosis. With advancements in the treatments for multiple myeloma, clinicians must have a high degree of suspicion for the

development of opportunistic infections, including Nocardia, in an effort to achieve early and effective diagnosis and treatment.

References:

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SN.	Year	location	Age/ sex	Occupation	Symptoms	Treatment	Diagnosis	Sample	Outcome
1	2021	Korea	64/	-	Smoked	trimethopri	Sigmoid	pleural	Alive on

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			M		for 20 years, cough	m/ sulfamethoxazole (80/160mg	colon cancer	fluid	going under treatment for colon cancer
2	2020	Germany	64/F	-	Dyspnea, productive cough, chest pain, and weight loss	Amoxicillin Ciprofloxacin imipenem and amikacin piperacillin/tazobactam and voriconazole	mimicking lung cancer	bronchoalveolar lavage	Alive
3	2019	Japan	70/ M	-	high-grade fever (38.0°C) and blood-stained sputum	Doripenem (DRPM) (1.5 g/day) PSL (35 mg/day) for radiation pneumonitis	right hilar squamous cell carcinoma (SCC) (cT3N3 M0, stageIIIB) pt. with Lung cancer	Sputum and BALF cultures	Died
4	2019	Belgrade, Serbia	70/ M	Retired	fever and cough. Chest x-ray	sulfamethoxazole and ceftriaxone	nocardial abscesses of the lung and	yellow, pus-like fluid	Unknown

					revealed lung lesion on the right side		brain lung cancer with brain metastases		
5	2019	Japan	76/M		cough, sputum production and chest discomfort	trimethoprim/ sulfamethoxazole levofloxacin	Colon cancer	transbronchial lung biopsy or cytology specimens	Alive
6	2018	Iran	73/F	-	diabetic foot ulcer, fever and vomiting	-	metastatic carcinoma brain tumor	brain biopsy test by PCR	Unknown
7	2017	France	59/M	-	dry cough	oral doxycycline	mimicking metastatic lung cancer	Brain sample cerebral abscesses	Unknown
8	2016	USA	71/M	-	fever and cough	trimethoprim-sulfamethoxazole and meropenem	Nocardiosis in a Multiple Myeloma	Bronchoscopy, bronchoalveolar lavage,	Unknown

								and transbronchial biopsies	
9	2014	Korea	56/M	-	underwent left lower lobe lobectomy for lung adenocarcinoma	piperacillin plus tazobactam trimethoprim-sulfamethoxazole	Nocardiosis mimicking lung cancer	sputum	Unknown
10	2004	Heraklion, Crete, Greece	52/M	-	severe dyspnea and productive cough	ceftazidime, 1 g amikacin, 500 mg and metronidazole, 600 mg	bacteremia in a patient with lung cancer	aerobic blood cultures	Alive

Table 1: Literature survey