Case study

An opportunistic blood stream 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, particularly in immunocompromised patients. Early identification and appropriate antibiotic susceptibility testing are necessary for prompt diagnosis of nocardiosis as it has highly-resistant antibiotic profile. This can improve the chances of survival of the patients. Here we present a case of fatal *N. farcinica* bacterimia in a 52-year-old man with brain cancer. He was admitted with complaints of fever, loss of recent memory along with increased aggressiveness and occasional fits. Blood cultures were taken at the time of hospital admission and *N. farcinica* was isolated and identified by automated culture and identification systems. Despite prompt antibiotic treatment, patient succumbed to death after 48 hrs.

Keywords: Antibiotic susceptibility, *Nocardia farcinica,* Nocardiosis, Aerobic gram-positive rods.

Introduction:

Nocardiosis is a rare opportunistic disease that primarily affects patients with impaired immune system. *N. farcinica*, the pathogen of bovine farcy, is one of the rare species of the genus *Nocardia* and it represents less than 3% of all cases of Nocardiosis. [1] This is being increasingly recognized as a cause of human infection, particularly in immunocompromised patients like cancer patients receiving chemotherapy or radiotherapy or patients with HIV infection. Nocardia is an aerobic Gram-positive rod that belongs to the class *Actinomycetia* 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. [1] The cancer patients residing in endemic rural areas where they have greater exposure and contact with moist soil and vegetations or those living under

unhygienic conditions are more prone to acquire infections by such opportunistic pathogens, leading to severe complications and fatal outcomes.

Case Report:

A 52-year-old diabetic male on oral hypoglycaemic drugs was admitted to Mahamana Pandit Madan Mohan Malviya Cancer Center, Varanasi (a unit of Tata Memorial Cancer Center) with complaints of headache, nausea, disorientation, confusion and loss of memory, for past 15 days. About 3 months ago he had been diagnosed with high grade brain tumor at Tata Memorial Hospital Mumbai, for which he underwent right parietal craniotomy and biopsy of splenial (corpus callosum) tumour and was planned for therapeutic radiation therapy. Patient was referred from Tata Memorial Hospital, Mumbai to a local radiotherapy centre at his native place but due to excessive aggressiveness of patient, the radiation therapy could not be given. The histopathology of brain biopsy tissue was suggestive of high grade infiltrating glial tumour of astrocytic morphology. After his surgey, the patient was put on levetiracetam 500mg twice daily along with intermittent steroids. 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 center, but due to progression of disease and associated symptoms, MRI brain could not be done. He acquired COVID-19 infection in January, 2022 and defaulted for further treatment for his malignancy. At the end of the month of February, he presented with complaints of drowsiness, confusion, low grade fever, increased aggressiveness, occasional fits and progressive dyspnoea for which he was admitted for supportive care in our hospital. On admission, he was observed to be acutely ill. The physical examination revealed a temperature of 38.4°C, respiratory rate of 40 per minute; blood pressure 90/60 mm Hg, and pulse rate 130 beats per minute. Laboratory data showed the following results: a white blood cell count of 13,870/mm^3 (neutrophils: 90.1%, lymphocytes: 1.8%, monocytes: 4.8%, and eosinophils: 0.1%), haemoglobin 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, total protein5.5 g/dL and albumin 3.0 g/dL. Paired sets of blood cultures were obtained and sent to laboratory, after which he was started on empirical intravenous antibiotics (cefaperazone-sulbactum, 1g tid; levofloxacin, 500 mg bid). In the next 24 hours, patient deteriorated further despite palliative care and antibiotic treatment but

his relatives got him discharged from the hospital against medical advice. Patient expired nearly 24 hours after his discharge from the hospital.

Blood cultures were performed with the BacT/Alert automated culture system. Positive blood cultures yielded Gram-positive branching rods in microscopy and were sub cultured onto 5% sheep blood, chocolate agar, and Sabouraud dextrose agar plates, which were incubated at 35°C.[2] Antimicrobial susceptibility testing was done using the disk diffusion method as per the reference [3] from Antibiotics were selected according to the recommendations for *Nocardia* in CLSI M24-2A, and included 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 reported as susceptible, intermediate susceptibility, or resistant based upon the reference from [3] *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were used as controls, showed susceptibility to ciprofloxacin (40mm), amoxicillin/clavulanic acid(25mm),minocycline(25mm), linezolid(40mm),tigecycline(24mm) andamikacin(35mm),butresistancetoertapenam(26mm),piperacillin/tazobactam(21mm),ceftriaxone(20mm),cefotaxime(25mm),cotrimoxazole(6mm),cefepime(10mm),meropenem(14mm),cefazolin(6mm),ceftazidime(6mm),gentamicin(16mm). Figure 1 The presumptive identification was done following the standard protocol and according to the findings of Gram stain, modified acid-fast stain, and the colony morphology on culture. *Nocardia* species were identified as grey-white colonies on solid culture media. Figure 2 The direct Gram stain from blood culture broth as well as from the colonies grown on solid culture media had shown thin, elongated and branching Gram-positive bacilli, which were also acid-fast in modified acid-fast staining. Figure 3 *Nocardia* species were further identified by MS identification using an automated VITEK-MS system (BioMerieux, France), which confirmed it to be *Nocardia farcinia.* [1]

Discussion:

Nocardiosis is an ancient disease that remains a public health problem in many impoverished locations worldwide. Genus *Nocardia* contains more than 219 species that have been described till date. The most commonly encountered species are *Nocardia brasiliensis, Nocardia cyriacigeorgica, Nocardia farcinica, and Nocardia nova*. *Nocardia steroides* is the most frequently found species causing non-cutaneous invasive disease while *Nocardia farcinica* is one

of the least common species. Nocardia infections are frequently life-threatening, particularly in patients with defective cell-mediated immunity. There are multiple risk factors that predispose patients to infection with these opportunistic pathogens, among which the conditions like cancer, infections like HIV or medications that suppress cell-mediated immunity predominate. Also, other patients with increased susceptibility to this infection include those with solid organ transplant and hematopoietic stem cell transplant recipients, and patients taking corticosteroids chronically. Since *Nocardia* infection occurs most commonly by inhalation of contaminated dust or by traumatic implantation of the bacteria, the lungs and the subcutaneous tissues are the usual sites of primary Nocardiosis. The organism can subsequently invade other sites by haematogenous dissemination and infective foci can develop in distant organs. Disseminated disease is potentially life-threatening, and mostly follows a primary lung infection. Once Nocardia spreads to the central nervous system, the mortality is 100%. The frequency of disseminated disease has been reported to range between 28% to 56%. Although it is believed that dissemination and metastatic infective foci formation are due to spread via bloodstream, yet the isolation of *N. farcinica* from blood cultures is rare. Because of its controversial status, *N. farcinica* was not described as a cause of human nocardiosis in literature for some years. Since its characterization as a distinct species, cases of *N. farcinica* infection are increasingly being reported. [2]

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). [1,2] [4-11] Specific risk factors were found in 94% of the patients mentioned in literature. The published literature of 10 cases represents data of patients with a mean age of 65.4 years (52-67 years).Interestingly; Most of them had a solid tumor with the following frequency: 60% lung cancer, 20% colon cancer, and 10% brain tumor while a minority were patients with multiple myeloma. Most of the cases presented with cough, fever, vomiting and weight loss. *Nocardia* incidence studies in cancer patients are scarce from India. Our case is remarkable as it represents the first reported case of *Nocardia* blood stream infection in a male patient with advanced brain tumor.

In most of the reported cases, the preliminary identification was *Nocardia spp.* and the exact identification was only performed later. Similarly, in our case *Nocardia farcinica* was initially

identified on the basis of microscopy, antibiotic sensitivity pattern and biochemical reaction susceptibility pattern and finally identified on automated culture and identification systems. Because of its specific multi-drug resistant pattern, the identification of *N. farcinica* have to be done as soon as possible as it is essential to guide the selection of appropriate antibiotics by the for clinicians and thus to improve survival of patients. Treatment should be advised in cancer and immunocompromised patients with increased risks of developing septicaemia.

In our patient the chemotherapy was withheld after diagnosing the blood stream *Nocardia* infection to balance both the need for cancer control and treatment of infection according to the antibiotic susceptibility pattern. But due to advanced nature of malignancy and palliative mode of cancer treatment, patient's relatives denied for the further admission of patient in the hospital and asked for the discharge against medical advice.

Conclusion:

Thus, patients with malignancy are more prone to acquire infection from soil and water. 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.

This is the first case of *Nocardia* infection in a patient from a remote poor area in North India. 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.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

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SN.	Year	location	Age/ sex	Occupation	Symptoms	Treatment	Diagnosis	Sample	Outcome

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1	2021[11]	Korea	64/M	-	Smoked for 20 years, cough	trimethoprim/ sulfamethoxazole (80/160mg	Sigmoid colon cancer	pleural fluid	Alive on going under treatment for colon cancer
2	2020[13]	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[14]	Japan	70/M	-	high-grade fever (38.0°C)	Doripenem (DRPM) (1.5 g/day) PSL (35	right hilar squamous cell carcinom	Sputum and BALF cultures	Died

					and blood-stained sputum	mg/day) for radiation pneumonitis	a (SCC) (cT3N3 M0, stageIIIB) pt. with Lung cancer		
4	2019[15]	Belgrade, Serbia	70/ M	Retired	fever and cough. Chest x-ray revealed lung lesion on the right side	sulfamethoxazole and ceftriaxone	nocardial abscesses of the lung and brain lung cancer with brain metastases	yellow, pus-like fluid	Unknown
5	2019[16]	Japan	76/ M		cough, sputum production and chest discomfort	trimethoprim/ sulfamethoxazole levofloxacin	Colon cancer	transbronchial lung biopsy or cytology specimens	Alive
6	2018[17]	Iran	73/F	-	diabetic foot ulcer, fever and vomiting	-	metastatic carcinoma brain	brain biopsy test by PCR	Unknown

							tumor		
7	2017[8]	France	59/M	-	dry cough	oral doxycycline	mimicking metastatic lung cancer	Brain sample cerebral abscesses	Unknown
8	2016[9]	USA	71/M	-	fever and cough	trimethoprim-sulfamethoxazole and meropenem	Nocardiosis in a Multiple Myeloma	Bronchoscopy, bronchoalveolar lavage, and transbronchial biopsies	Unknown
9	2014[10]	Korea	56/M	-	underwent left lower lobe lobectomy for lung adenocarcinoma	piperacillin plus tazobactam trimethoprim-sulfamethoxazole	Nocardiosis mimicking lung cancer	sputum	Unknown
10	2004[11]	Heraklion, Crete, Greece	52/M	-	severe dyspnea and productiv	ceftazidime, 1 g amikacin, 500 mg and	bacteremia in a patient with lung	aerobic blood cultures	Alive

					e cough	metronidazole, 600 mg	cancer		

Table 1: Literature survey

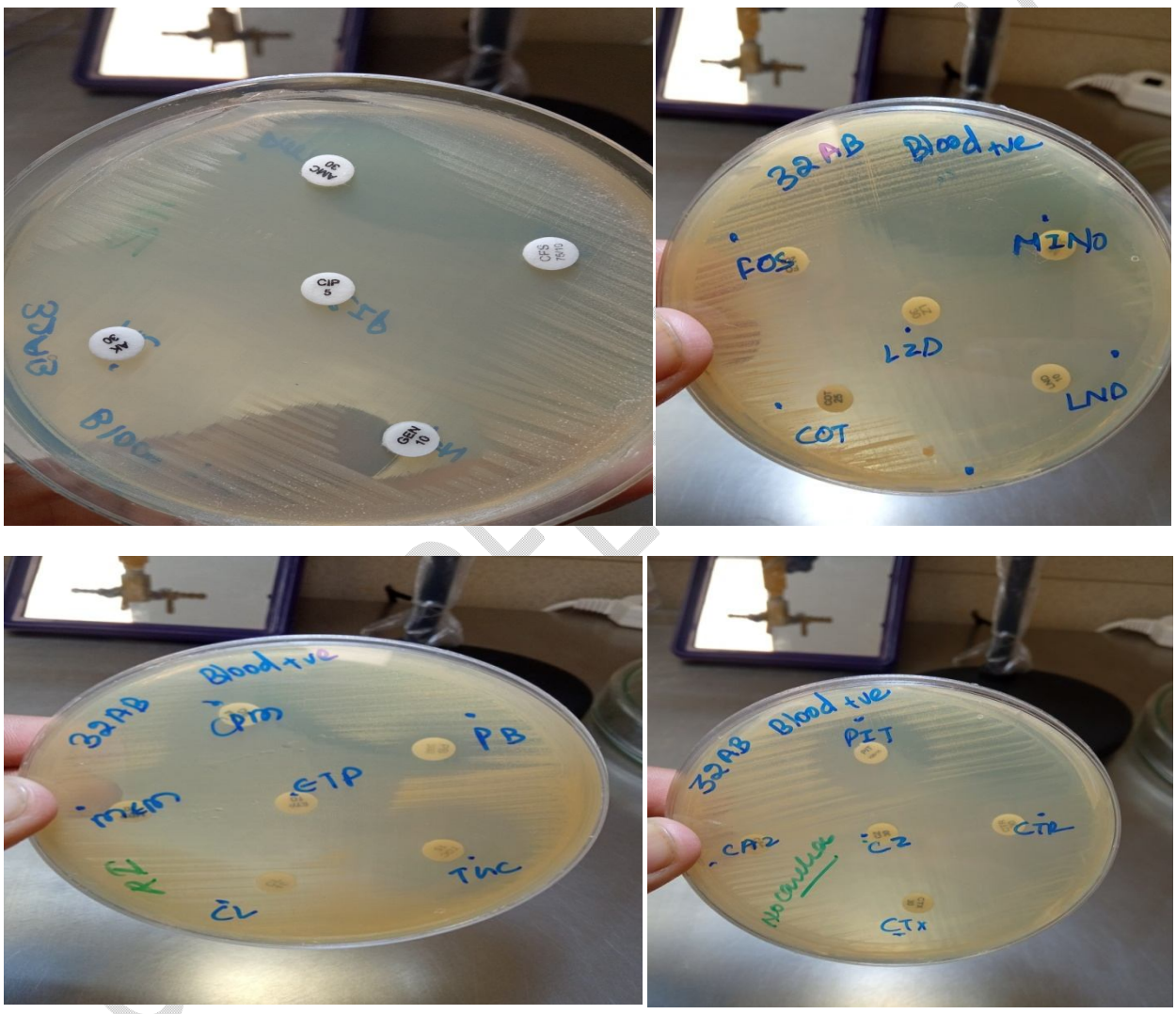

Figure 1- Antimicrobial susceptibility testing using the disk diffusion method showed susceptibility. (Reference-3)

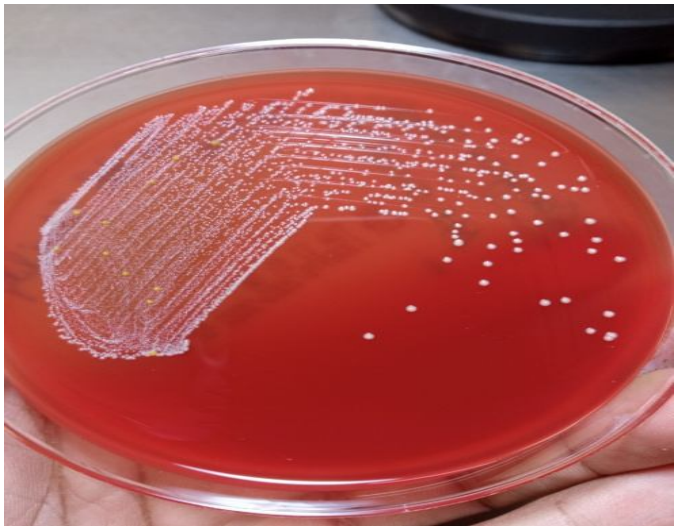

Figure 2 - *Nocardia* species were identified as grey-white colonies on solid culture media.

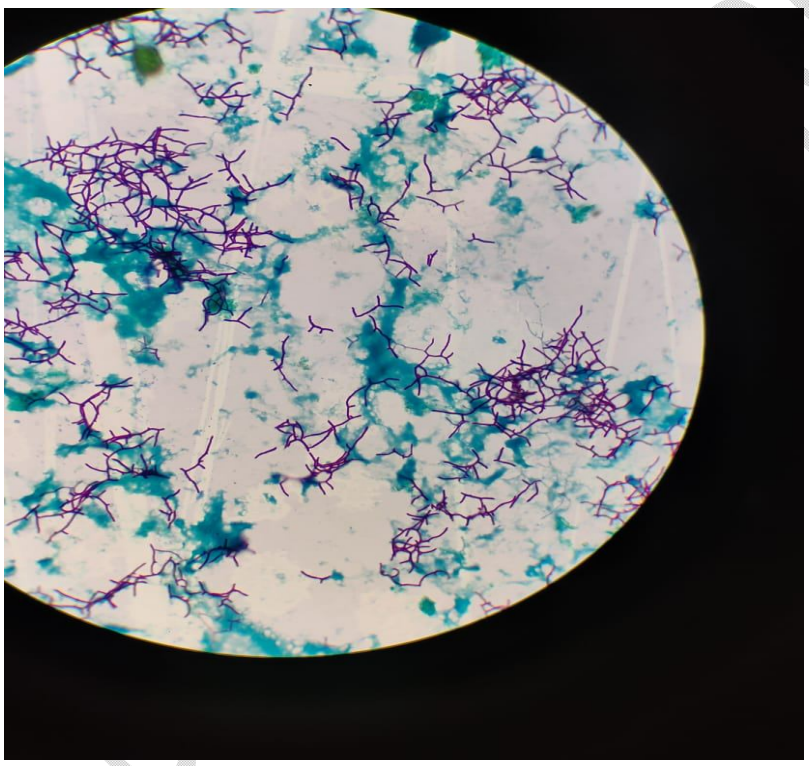

Figure 3 - Acid-fast in modified acid-fast staining.