Isolated Cerebral Nocardiosis Otitidiscaviarum in a Child with relapsed B-Lymphoblastic Leukemia: Diagnostic and Therapeutic Challenges Including Relevant Review of Literature

Sir,

Nocardia is responsible for 1.5% of cerebral abscess (CA) worldwide.[3] This ubiquitous bacteria have high mortality (33%) with variable presentations i.e., acute–chronic and isolated to disseminated.[2] Cerebral nocardiosis (CN) lacks classical signs on neuro-imaging and clinical and laboratory examination and is often diagnosed after surgical excision, which lends to a diagnostic delay and increased mortality. We describe a case of CN in a child with B-acute lymphoblastic leukemia (B-ALL), who had isolated cerebral localization, negative initial microbiological examination, and poor response to cotrimoxazole (CTX), which posed a diagnostic dilemma.

A 10-year-old male with precursor B-ALL presented with seizures during maintenance chemotherapy instituted as part of the Indian Collaborative Childhood Leukemia group (ICiCle) protocol.[3] No antecedent fever or focal neurological deficits were noted. Neuroimaging revealed a well-demarcated, multi-loculated lesion measuring 7.5 × 5.2 × 5.4 cm in the left temporoparietal lobe with peri-lesional edema [Figure 1a]. Decompressive craniotomy with excision was done on suspicion of leukemic infiltration. The tissue sent for histopathology evaluation (HPE) showed an abscess composed of fibro-collagenous tissue with scanty chronic inflammation and few hemosiderin-laden macrophages. Pus subjected for fungal and bacterial culture was sterile. After the completion of chemotherapy, he presented with bone marrow and testicular relapse. Subsequently, he developed facial nerve palsy, and neuroimaging showed residual lesion now in the left parieto-occipital region [Figure 1b]. Intravenous vancomycin and meropenem were administered for 4 weeks. Meanwhile, in view of raised intracranial pressure, pus drainage was done and sent for culture. The latter was sterile, and the real-time polymerase chain reaction (PCR) performed for Mycobacterium species was negative. The bits of the cyst wall sent for HPE revealed large central areas of liquefactive necrosis mixed with neutrophils and debris. The surrounding white matter exhibited reactive gliosis. No granulomas were seen, and histochemical stains done for fungus and acid-fast bacilli were negative. Modified (1%) Ziehl–Neelsen (ZN) stain showed numerous thin (<1 mm width) filamentous, beaded bacilli exhibiting branching patterns. Gram and Grocott’s methenamine silver (GMS) stains were also consistent with Nocardia [Figure 2]. The bacilli were clinging to the cyst wall and were absent in the central necrotic areas, explaining the negativity of the culture and PCR. Following intravenous CTX × 2 weeks (@ 15 mg/kg/day in three divided doses), the oral CTX was supplemented with minocycline (50 mg twice a day). Repeat imaging showed an increase in the number of lesions involving the tempo-occipital region [Figure 1c]. Pus showed similar bacilli which were weakly Gram-positive and acid-fast on Kinyon’s modified ZN stain. Samples inoculated onto sheep blood agar (5%–10%) showed whitish-dry cerebriform colonies after 3 days of incubation [Figure 2]. Furthermore, the isolate was identified as Nocardia otitidiscaviarum by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Microflex LT Biotyper, Bruker Daltonics, Germany). Basic Local Alignment Search Tool (BLAST) analysis (https://blast.ncbi.nlm.nih.gov) of the sequence showed 99.83% identity with the sequence of Nocardia otitidiscaviarum strain (ATCC 14629i; Sequence ID.
AY756528). This patient developed bone marrow recurrence of ALL and was discharged on palliative therapy.

*Nocardia* is a rare, life-threatening cause of cerebral abscess, which is acquired through inhalation or direct inoculation. Hence, pulmonary and cutaneous involvement are the commonest manifestations. This bacterium is highly neurotropic and up to 40% of cases with hematogenous dissemination have central nervous system (CNS) involvement. Conversely, the isolated involvement of the CNS is uncommon, seen in 5% of cases. Anagnostou T et al. analyzed 84 CN cases and documented neurologic abnormalities as the commonest (51% cases) presentation followed by headache, fever, distorted mental status, seizures (in 28%), vision abnormalities, ataxia, and personality changes. The index patient presented with non-localizing signs at first and developed focal deficit with disease progression. There was no history of fever or headache in our patient. As the patient was on follow-up for ALL, the appearance of intracranial mass lesions was thought to be leukemic infiltration. The diagnosis of CN was suggested on histological examination on the second biopsy as the initial biopsy yielded only a fibrous wall. Out of 17 cases of cerebral abscesses, this was the second case of Nocardial etiology.
Nocardia commonly infects those with hematological malignancies than solid malignancies. CN has been described in cases of myeloma, leukemias (lymphoblastic, myeloid, hairy cell, chronic lymphocytic leukemia), lymphomas such as diffuse large B-cell lymphoma (DLBCL), and Hodgkin lymphoma [Table 1].[7-9] Majeed A. described CN in 3 of 10 patients with hematological neoplasms having a protracted clinical course similar to the index case. Older age and a longer duration of illness between leukemia diagnosis and infection were observed in the cases with fatal outcomes.[10]
Species-wise, *N. asteroides* was the most common species before the molecular era. With the advent of gene sequencing, several less common species such as *N. faricinica*, *N. cyriacigeorgica* in <5% cases, and *N. transvalensis*, *N. brasiliensis*, and *N. otitidiscaviarum* have been reported in CA in <2% cases.\(^{[1]}\) Species identification is indispensable in modern medicine, which focuses on personalized therapy. For e.g., the index case responded poorly to CTX and minocycline and was found to be resistant to sensitivity testing. However, it was sensitive to gentamycin, amikacin, and imipenem. This led to a delay of 3 months in starting the appropriate therapy from the time of first seizure. Other reasons for the chronic intractable course [Figure 3] and suboptimal response could be due to the thickened fibrotic wall, which could have impeded the delivery of the antibiotics.

A high index of suspicion for Nocardial etiology should be reserved for cases harboring prolonged lymphocyte dysfunction even if there is no pulmonary lesion. As *Nocardia* is difficult to detect on smears, and culture combination of histopathology with species identification by molecular techniques is essential for the timely initiation of sensitive antibiotics, treatment (and prophylaxis) for Nocardial brain abscess using a combination of a carbapenem and CTX should be initiated in such cases.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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