Central nervous system abscesses are rare sequelae in immunosuppressed and immunocompromised states and can present a significant challenge in their management. Neuroimaging is an important tool for timely diagnosis and intervention. While the differential diagnosis for new lesions on neuroradiological imaging of immunosuppressed patients typically includes infections and neoplasms, image-based heuristics to differentiate the two has been shown to have variable reliability.

The authors describe 2 rare CNS infections in immunocompromised patients with atypical physical and radiological presentations. In the first case, a 59-year-old man, who had recently undergone a renal transplantation, was found to have multifocal *Nocardia amikacinitolerans* abscesses masquerading as neoplasms on diffusion-weighted imaging (DWI); in the second case, a 33-year-old man with suspected recurrent Hodgkin’s lymphoma was found to have a nonpyogenic abscess with cytomegalovirus (CMV) encephalitis.

As per review of the literature, this appears to be the first case of brain abscess caused by *N. amikacinitolerans*, a recently isolated superbug. Despite confirmation through brain biopsy later on in case 1, the initial radiological appearance was atypical, showing subtle diffusion restriction on DWI. Similarly, the authors present a case of CMV encephalitis that presented as a ring-enhancing lesion, which is extremely rare. Both cases draw attention to the reliability of neuroimaging in differentiating an abscess from a neoplasm.

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**KEYWORDS** brain abscess; *Nocardia amikacinitolerans*; cytomegalovirus; CMV encephalitis; CNS infection; immunocompromised

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**Case Reports**

**Case 1: Nocardia amikacinitolerans Brain Abscess**

**History and Physical Examination**

A 59-year-old male dentist presented to our emergency department with relatively sudden-onset but progressive diplopia, headache, and ataxia of 1-week duration. The double vision was relieved when covering one eye at a time. The headache was frontal, throbbing in nature, and transiently relieved by acetaminophen. The patient was evaluated by an ophthalmologist who suspected ocular palsy...
and advised the patient to see a neurologist. The patient’s medical history was significant for end-stage renal disease and hemodialysis for 8 years, a renal transplant 8 weeks prior to admission, and steroid-induced diabetes mellitus and hypertension diagnosed after the transplantation. The extensive list of medications was notable for trimethoprim/sulfamethoxazole (TMP/SMX), mycophenolate, prednisone, tacrolimus, and valganciclovir. The patient had no fatigue, fever, or weight loss and reported full adherence to medications. Physical examination showed a patient who was alert and oriented to time, place, and person, with right oculomotor nerve palsy and left facial droop. Laboratory workup was positive for normocytic normochromic anemia (hemoglobin 10.2 g/dl), mild thrombocytopenia (platelet count 118,000/μl), and low absolute lymphocyte count (150/μl). The patient’s white blood cell count was 8400/μl, with an absolute neutrophil count of 7200/μl.

Imaging Studies

Noncontrast brain CT revealed a subtle right frontal patchy hypodensity with surrounding edema, in addition to a right midbrain-thalamic 15-mm hemorrhagic lesion causing ventricular effacement and 2- to 3-mm midline shift to the left. MRI with and without contrast showed a largely homogeneously enhancing 2-cm mass in the right frontal subcortex and a 2-cm right thalamic mass demonstrating heterogeneous enhancement with punctate central nonenhancing areas suggestive of necrosis (Fig. 1). Both masses were surrounded by vasogenic edema, with the thalamic mass causing a 2- to 3-mm midline shift and mild hydrocephalus due to aqueductal compression. Gradient echo MRI showed minimal hemorrhage in the thalamic mass. DWI showed subtle restricted diffusion in both lesions. The differential diagnosis was largely limited to neoplastic and infectious entities, with the most likely neoplastic lesions being either metastatic disease or lymphoma. A full-body CT scan showed no suspicious masses suggestive of widespread metastatic disease; hence, an open brain biopsy of the frontal lobe lesion was planned.

Operative and Postoperative Course

Due to the possibility of lymphoma, dexamethasone was not administered pre- or intraoperatively so as not to compromise the yield of the biopsy specimen. The lesion was approached via a standard right frontal craniotomy made just above the mass using neuronavigation. We entered the mass at its most superficial location. On gross inspection, emulsified brain tissue was seen, and a whitish viscous fluid oozed out of the friable mass, both of which were extracted for histopathology and cultures. The patient tolerated the operation without any issues. The surgical pathology report showed an inflammatory abscess.
(dense neutrophilic infiltration) with clusters of gram-positive beaded filamentous microorganisms morphologically compatible with *Nocardia*. Microbiological and sensitivity cultures identified *Nocardia amikacin intolerans* the species. The patient was started on TMP/SMX and imipenem. On follow-up 1 month after surgery, the patient reported improvement of his ataxia but not the double vision, and imaging showed persistent vasogenic edema around the old lesion in the frontal lobe—most likely postbiopsy changes—with shrinkage of midbrain-thalamic mass. His white blood cell count and absolute neutrophil count were normal (7800/µl and 7300/µl, respectively) but absolute lymphocyte count (0.31/µl) and platelets (87,000/µl) remained low. The patient is currently following up with hematology and department of infectious diseases.

**Case 2: Nonpyogenic Abscess With Cytomegalovirus Encephalitis**

**History and Examination**

A 33-year-old man, with a distant history of 6 cycles of chemotherapy for Hodgkin’s lymphoma and subsequent autologous bone marrow transplantation after a relapse, presented to an outside hospital with fever, cough, headaches, and lethargy that began months prior. During this time, the patient also reported a 40-pound weight loss due to decreased appetite, as well as frequent subjective fevers. At the outside hospital, workup revealed acute sinusitis and pneumonia; incidental findings included hypogammaglobulinemia, new mediastinal and bilateral hilar lymphadenopathy, mild splenomegaly, and a new right periventricular frontal lobe ring-enhancing lesion. The patient had previously been following up with an oncologist, and his lymphoma had been in remission until he was lost to follow-up in 2009. After several courses of antibiotics, the patient was transferred to our institution for neurosurgical evaluation and biopsy of the new intracranial lesion.

The patient complained of only occasional moderately severe headaches, along with improved residual symptoms of pleuritic chest pain and cough from the pneumonia. Interestingly, he had seen his optometrist within the previous 2 months for a routine evaluation, and she identified papilledema, for which she recommended brain imaging. The patient was made aware of this and did not follow-up accordingly. Physical examination revealed a slight left-sided pronator drift, left superior homonymous quadrantanopia, and blunt visual affect. The patient denied any gait or balance disturbance, visual complaints, sensation disturbances, or weakness. Laboratory workup was unremarkable other than a slightly elevated absolute lymphocyte count of 3500/µl (reference range 850–3000/µl).

**Imaging Studies**

MRI of the brain with and without contrast revealed a deep-seated 4-cm irregular rim-enhancing lesion in the right inferior frontal lobe involving the caudate and adjacent ganglionic structures (Fig. 2). There was some mass effect displacing the optic chiasm noted in the report. Also noted was surrounding vasogenic edema that extended into the region of the corpus callosum. The mass showed a hemosiderin ring but no central restricted diffusion. The differential diagnosis suggested by the imaging included a neoplasm, hematoma, or atypical nonpyogenic abscess with encephalitis. Repeat MRI with Stealth protocol was performed at this institution and confirmed the findings.

**Operative and Postoperative Course**

After the patient was counseled regarding the initial findings on brain imaging, he agreed to undergo a stereotactic needle biopsy of the mass. The needle biopsy was recommended because of the high-risk location of the mass and the diagnostic uncertainty. In the operating room, a right frontal trajectory was chosen to access the mass. Then using MRI neuronavigation, a biopsy needle was passed along the planned trajectory path into the lesion. Examination of a specimen taken from this approach revealed grossly abnormal tissue. Several samples were taken, and evaluation of frozen sections confirmed obvious lesional tissue. The patient tolerated the procedure well and was medically cleared for discharge the following day. The pathology report on the specimens collected during the biopsy revealed patchy dense lymphoid infiltrate composed of small, mature cells without overt signs of atypia. No necrosis was identified. The overall features of the sample were consistent with a chronic inflammatory infiltrate without evidence of any lymphoproliferative disorder. Neuropathology revealed scattered enlarged neuroglial cells with viral inclusions that stained immunologically positive for cytomegalovirus (CMV) (Figs. 3 and 4).
During an outpatient follow-up visit 3 weeks after surgery, the patient was clinically stable and neurologically intact. He was referred to infectious diseases for management of the CMV infection, where he was started on a regimen of oral valganciclovir and scheduled for follow-up brain MRI.

Discussion

Despite advances in imaging, neurosurgical technique, and antimicrobial therapy, brain abscesses remain a challenging entity that are often associated with a grim prognosis. They typically affect individuals with predisposing factors like immunocompromise (e.g., HIV, hematopoietic malignancy, chronic steroid use, and, more recently, a growing litany of immunosuppressive medications), breach of the blood-brain barrier (e.g., due to cranial surgery or sinusitis), or a systemic source of infection (e.g., septic emboli of infective endocarditis). Pathogens can access the brain through contiguous spread in roughly 50% of cases, hematogenous seeding in about 33%, and an unknown mechanism in the remaining cases. The pathological process begins with a focus of cerebritis that evolves into a purulent lesion surrounded by a well-vascularized fibrotic capsule. Patients with brain abscesses can present with any number of symptoms. Headache, fever, and focal neurological deficits are among the most common presenting symptoms, but they are infrequently seen together.

There have been a number of abscess-causing organisms described in the literature. In 2014, Brouwer and colleagues published a systematic review and meta-analysis of the clinical characteristics, causal organisms, and outcomes of brain abscesses in 123 studies from 1935 to 2012. Their analysis of 9699 cases revealed a total of 85 different causal organisms. Most commonly among them were Streptococcus and Staphylococcus spp., which comprised 34% and 18% of the cases analyzed, respectively. Of the less frequently reported causal organisms in the meta-analysis, Nocardia, Enterococcus, Mycobacterium tuberculosis, parasites, and fungi were the most rare. As the authors pointed out, 86% of the cases in their analysis shared the characteristic of an underlying predisposing condition like immunocompromise or distant primary infectious foci. As might be expected, patients with the predisposing condition of an underlying immunocompromised state are at an increased risk of developing a brain abscess with a rare causal organism.

Some insight as to the causal organism can be gleaned from neuroradiological presentation. For example, parasitic abscess typically presents as small multifocal lesions, whereas bacterial and fungal abscesses tend to be larger, singular, or few in number. Recent investigations into susceptibility-weighted MRI sequences have been helpful in identifying differentiating characteristics between bacterial and fungal abscesses.

As will be discussed, neuroradiological techniques can be useful for differentiating an abscess from other etiologies of intracranial mass lesions. In our case series, we presented 2 unique cases. The first case involved a pyogenic abscess exhibiting unusual radiological features on DWI,
and the second involved CMV encephalitis presenting as a focal abscess, another extremely rare presentation. Our aim here is to increase awareness of these rare intracranial pathogens and discuss the reliability of state-of-the-art neuroimaging in differentiating between intracranial abscesses and neoplasms. Together, these cases demonstrate the need to prioritize an abscess in the differential diagnosis of new intracranial mass lesions in patients with predisposing factors such as an immunocompromised state and also, when an abscess is suspected in these patients, to consider both common and unlikely causal agents.

Nocardia amikacinitolerans

Nocardia is a rare bacterial opportunistic pathogen, responsible for around 1%–2% of all brain abscesses, with a reported mortality rate reaching up to 66% compared with < 10% in other bacterial abscesses. The abscesses are weakly acid-fast, gram-positive, branching filamen-
tous aerobes found ubiquitously in the soil all over the planet. The most common culprits in humans are N. asteroides, N. brasiliensis, and N. caviae. Nocardia can enter the body through inhalation or direct skin inoculation, which usually causes a self-limiting asymptomatic infection that goes unnoticed in the immunocompetent individual. However, immunocompromised states (e.g., post–organ transplant as in our patient) allow primary infection to propagate into systemic bacteremia, which has a particular affinity to spread to the nervous system. CNS involvement has been observed in almost half of disseminated nocardiosis cases.

In 2013, Ezeoke et al. isolated a novel species of Nocardia from eye and lung sources in 5 patients. Antimicrobial susceptibility testing revealed that all 5 isolates were resistant to amikacin, ciprofloxacin, and clarithromycin, with amikacin resistance being the highest. Interestingly, resistance to amikacin among people with Nocardia is rare, making it a differentiating characteristic for this species, hence the nomenclature. We did not find any previous reports of infection with this species. The choice of appropriate antibiotic for this species can be considered between amoxicillin/clavulanate, ceftriaxone, imipenem, linezolid, and TMP/SMX. In our patient, a combination of TMP/SMX and imipenem seemed efficacious given the radiologically proven shrinkage of the thalamic lesions on sequential MR images.

The Role of Neuroimaging in Brain Abscesses

Brain abscesses appear as ring-enhancing lesions, with a hypointense rim on T2-weighted MRI being a common feature shared with necrotic glioblastomas. However, conventional MRI alone can be inadequate in differentiating an abscess from other intracranial pathologies, especially neoplasms. This is further compounded by the frequent absence of reliable symptoms in brain abscess like fever and altered mental status. Therefore, MRI sequences such as DWI and ADC maps are considered most telling in the case of cerebral abscess. Brain abscesses usually restrict on DWI with corresponding low ADC values; this leads to the characteristic “white” appearance on DWI images and “dark” appearance on ADC maps. In our case, however, the abscess showed only subtle diffusion restriction on DWI, which gave the initial impression of the second most likely diagnosis, brain metastases. Open biopsy later confirmed a brain abscess. This raises the important question as to whether certain abscesses fail to cause characteristic DWI restriction and whether this failure is based on organism type or perhaps the age or state of the abscess. In light of our case, we reviewed the literature for reported nocardial abscess appearance on DWI. Table 1 demonstrates that 10 (59%) of 17 cases

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Age (yrs), Sex</th>
<th>Nocardial Species</th>
<th>Capsule on DWI</th>
<th>ADC Maps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamada et al., 2005</td>
<td>1</td>
<td>58, F</td>
<td>NS</td>
<td>Heterogeneous</td>
<td>NS</td>
</tr>
<tr>
<td>Zakaria et al., 2008</td>
<td>1</td>
<td>40, M</td>
<td>N. asteroides</td>
<td>Hyperintense</td>
<td>NS</td>
</tr>
<tr>
<td>Hashimoto et al., 2008</td>
<td>7</td>
<td>77, F</td>
<td>N. nova</td>
<td>Hyperintense</td>
<td>Low</td>
</tr>
<tr>
<td>Roca &amp; Merino, 2010</td>
<td>1</td>
<td>33, M</td>
<td>N. nova</td>
<td>Hyperintense</td>
<td>NS</td>
</tr>
<tr>
<td>Pyatigorskaya et al., 2010</td>
<td>1</td>
<td>59, NS</td>
<td>N. abscessus</td>
<td>Hyperintense</td>
<td>Low</td>
</tr>
<tr>
<td>Aljani et al., 2013</td>
<td>1</td>
<td>31, F</td>
<td>NS</td>
<td>Hyperintense</td>
<td>NS</td>
</tr>
<tr>
<td>Kranick &amp; Zerbe, 2013</td>
<td>1</td>
<td>18, M</td>
<td>N. transvalensis</td>
<td>Hyperintense</td>
<td>Low</td>
</tr>
<tr>
<td>Nandhogopal et al., 2014</td>
<td>1</td>
<td>16, M</td>
<td>NS</td>
<td>Hyperintense</td>
<td>Low</td>
</tr>
<tr>
<td>Pamukçuoğlu et al., 2014</td>
<td>2</td>
<td>61, F; 60, F</td>
<td>N. cyriacigeorgica</td>
<td>Hyperintense; hyperintense</td>
<td>Low; low</td>
</tr>
<tr>
<td>Beuret et al., 2015</td>
<td>2</td>
<td>64, F; 68, M</td>
<td>N. farcinica</td>
<td>Hyperintense; hyperintense</td>
<td>High; low</td>
</tr>
<tr>
<td>Molière &amp; Krémér, 2015</td>
<td>1</td>
<td>65, F</td>
<td>N. nova</td>
<td>Hyperintense</td>
<td>Low</td>
</tr>
<tr>
<td>Stefanik, 2015</td>
<td>1</td>
<td>59, M</td>
<td>NS</td>
<td>Hyperintense</td>
<td>NS</td>
</tr>
<tr>
<td>Majeed et al., 2017</td>
<td>1</td>
<td>72, M</td>
<td>N. kroppenstedtii</td>
<td>Hyperintense</td>
<td>Low</td>
</tr>
<tr>
<td>Chaudhari et al., 2017</td>
<td>1</td>
<td>75, M</td>
<td>N. farcinica</td>
<td>Hyperintense</td>
<td>Low</td>
</tr>
<tr>
<td>Yamamoto et al., 2017</td>
<td>1</td>
<td>73, M</td>
<td>N. araoensis</td>
<td>Hyperintense</td>
<td>Isointense</td>
</tr>
<tr>
<td>Present case</td>
<td>1</td>
<td>59, M</td>
<td>N. amikacinitolerans</td>
<td>Heterogeneous</td>
<td>Heterogeneous</td>
</tr>
</tbody>
</table>

NS = not stated.
TABLE 2. Details of reported cases of cerebral mass lesions due to CMV in patients with AIDS

<table>
<thead>
<tr>
<th>Age (yrs), Sex</th>
<th>History of AIDS</th>
<th>CD4+ Cells/μl</th>
<th>Diagnosis</th>
<th>Clinical Presentation</th>
<th>Brain CT/MRI</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyer et al., 1995</td>
<td>32, M</td>
<td>Yes</td>
<td>Fever, Sz, bilat limb weakness</td>
<td>Single hemispheric lesion</td>
<td>Brain biopsy</td>
<td>Ganciclovir</td>
<td>Death 3 mos after diagnosis</td>
</tr>
<tr>
<td>Dyer et al., 1995</td>
<td>31, M</td>
<td>No</td>
<td>Fever, Sz, confusion, myelopathy, pneumonitis, retinitis</td>
<td>Single hemispheric lesion</td>
<td>CSF PCR</td>
<td>Ganciclovir &amp; then foscarnet</td>
<td>Death 5 mos after symptom onset</td>
</tr>
<tr>
<td>Moulignier et al., 1996</td>
<td>39, M</td>
<td>NA</td>
<td>Fever, HA, hemiparesis, frontal lobe syndrome</td>
<td>Two hemispheric lesions</td>
<td>Brain biopsy &amp; Foscarnet</td>
<td>Ganciclovir &amp; then foscarnet</td>
<td>Death 10 wks after symptom onset</td>
</tr>
<tr>
<td>Moulignier et al., 1996</td>
<td>34, M</td>
<td>No</td>
<td>HA, hemiparesis, aphasia, retinitis, colitis</td>
<td>Single hemispheric lesion</td>
<td>Brain biopsy</td>
<td>Foscarnet &amp; then ganciclovir</td>
<td>Death 6 mos after symptom onset</td>
</tr>
<tr>
<td>Bassil &amp; William, 1997</td>
<td>31, M</td>
<td>Yes (retinitis)</td>
<td>Single hemispheric lesion</td>
<td>Brain biopsy</td>
<td>Ganciclovir</td>
<td>Alive 4 mos after hospital discharge</td>
<td></td>
</tr>
<tr>
<td>Huang et al., 1997</td>
<td>51, M</td>
<td>Yes</td>
<td>HA, hemiparesis, cerebellar syndrome</td>
<td>Single cerebellar lesion</td>
<td>Autopsy</td>
<td>No Treatment</td>
<td>Death 4 mos after admission</td>
</tr>
<tr>
<td>Vidal et al., 2003</td>
<td>39, F</td>
<td>No</td>
<td>Fever, Sz, psychomotor slowing, pulmonary mass, perivaginal ulcers</td>
<td>Single hemispheric lesion</td>
<td>Brain biopsy</td>
<td>No Treatment</td>
<td>No Treatment</td>
</tr>
</tbody>
</table>

HA = headache; NA = not available; PCR = polymerase chain reaction; Sz = seizure.

High signal intensity on DWI with low ADC values for cerebral abscesses was first reported by Ebisu et al., with many subsequent studies reporting similar findings. In a meta-analysis Xu et al. found that DWI had a high sensitivity (0.95) and specificity (0.94) for differentiating brain abscesses from other cystic brain masses, showing it is a reliable method in detecting pyogenic brain abscesses. However, there are exceptions. Cases that have involved absent diffusion restriction on DWI have been reported before in patients with brain abscesses. This unusual radiological appearance could be attributed to several factors that can alter pus composition and viscosity, such as early initiation of antimicrobial therapy, failure of adequate neutrophilic infiltration due to immunocompromise, the age of abscess, and even the type of infecting organism. For example, hypointensity and heterogeneous appearance on DWI have been reported with fungal and tuberculous abscesses.

CMV Encephalitis

CMV is a Herpesviridae virus that is common in the population as a latent infection. Primary infection with CMV is typically subclinical and becomes latent in the immunocompetent individual. Reactivation of dormant CMV is more frequent in critically ill patients and can manifest as a systemic or end-organ disease like pneumonitis or gastroenteritis. While in the past CMV recurrence or infection was most typically seen in patients with AIDS, tissue-invasive CMV infection has had an increasing incidence among individuals who have undergone solid-organ transplant, hematopoietic stem cell transplant, and other immunosuppressed or immunocompromised states.

CMV brain infection, most commonly manifesting as encephalitis or ventriculitis, is a rare and deadly complication in immunocompromised patients and requires immediate treatment. Because of the high mortality and morbidity rates, current recommendations suggest proactive screening for CMV and treatment for anyone with a detectable serological or CSF viral load. Typical findings on MRI that suggest CNS disease include white matter nodular signal abnormalities, ventriculitis with accompanying subependymal lesions on T2-weighted FLAIR images, the classic “Owl’s sign” seen in CMV ventriculitis, and, rarely, a focal mass lesion. There is a paucity of data regarding DWI findings, and, as suggested elsewhere, this is likely because DWI was not routinely available in the era before highly active antiretroviral therapy. Overall, CMV recurrence typically carries a poor prognosis, and therapeutic options are limited to only a few antiviral agents.

Interestingly, the CMV brain abscess in our patient was incidentally discovered during workup for acute sinusitis, which revealed the right ganglionic lesion. The incidence of CMV encephalitis, especially in a patient without AIDS, is extremely rare. Moreover, there are only 8 previously documented cases of intracranial CMV masses, all of which occurred in patients with significantly low CD4-positive T-lymphocyte counts (8–81 cells/μl). As shown in Table 2, all these patients had AIDS, were significantly symptomatic, and died soon after diagnosis. Characteristics of lesions on MRI were also similar to those of our cerebral abscesses, showing true restricted diffusion, i.e., hyperintensity on DWI and low signal on ADC maps.
patient’s: focal, most often single, supratentorial ring-enhancing lesions that could not be distinguished as either neoplasm or infection. Unfortunately, T- and B-cell counts were never measured during the patient's hospitalization; however, the patient has multiple risk factors for CMV recurrence: possible cellular immunosuppression secondary to recurrent lymphoma, known hypogammaglobulinemia, and a history of autologous hematopoietic stem cell transplantation. The pathophysiology behind mass lesion development is not well understood, but immunoglobulin deficiency, especially in bone marrow transplant recipients, may play a role.24,25,44

Conclusions

**Nocardia amikacinitorans** is a newly isolated opportunistic bacterial superbug that is highly resistant to amikacin but is sensitive to TMP-SMX and imipenem, among others. Functional MRI sequences play a fundamental role in the timely diagnosis and management of brain abscesses. True restricted diffusion—defined as hyperintensity on DWI and low signal on ADC maps—is an important clue to distinguish brain abscesses from other ring-enhancing lesions. However, the absence of diffusion restriction on DWI does not preclude the possibility of an abscess, which should stay high on the list of differential diagnoses, especially in an immunocompromised host. Furthermore, we describe the ninth reported case of intracranial CMV abscess in a patient with suspected recurrent lymphoma—the first case in a patient without AIDS. These 2 case studies emphasize the importance and limitations of neuroimaging in the diagnosis of CNS infections and the need to consider rare causal agents in immunocompromised patients.

References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Hanft, Quinoa, Narayan. Acquisition of data: Quinoa, Jumah, Xiong, Nanda. Drafting the article: all authors. Critically revising the article: Hanft, Quinoa, Narayan. Approved the final version of the manuscript on behalf of all authors: Hanft. Administrative/technical/material support: all authors. Approved the final version of the manuscript on behalf of all authors: Hanft. Study supervision: Hanft.

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