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Teaching Case

Streptococcus Intermedius: A Mimicker of Brain Metastases and A Potential Pitfall for Radiation Oncologists

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Introduction

Brain metastases are the most common etiology of tumors found in the central nervous system.[1] Radiation therapy has become a cornerstone of treatment for brain metastases.[2,3] However, diagnosing the etiology of brain lesions can present a challenge to clinicians owing to the diversity of metastatic-mimicking pathologies, such as abscesses, vasculitides, demyelinating lesions, and granulomatous diseases.[4,5] A conscientious and fastidious approach to the diagnosis and treatment of brain metastases is essential to avoid inappropriate procedures and rushed empirical treatments. Mimickers of metastasis should always be considered in the differential diagnosis of the consulting radiation oncologist.

Streptococcus intermedius, a member of the anginosus group, is a viridians streptococcal species.[6] As part of the normal flora found in the oral cavity and gastrointestinal tract, healthy individuals typically do not develop an invasive infection with a member of this group.[7,8] Risk factors for developing invasive infections include sinusitis, congenital heart disease, dental disease, oral procedures, liver cirrhosis, and pulmonary disease.[9,10] *Streptococcus intermedius* is known for causing abscesses in the liver, lung and brain; they are normally solitary and often require surgical intervention.[8] This case report highlights *Streptococcus intermedius* as a mimicker of brain metastasis.

Case

A 49-year-old male patient presented to urgent care with 2 weeks of dyspnea, cough, fatigue, retro-orbital headache, and generalized body aches. His medical history included polycythemia, seasonal allergies, hypertension, hyperlipidemia, and prediabetes. He had no history of smoking, tobacco, or vaping use. Prior COVID-19 testing was negative. Owing to hypoxemia and a history of pulmonary emboli, the patient was transferred to the emergency department for further evaluation. A computed tomography (CT) pulmonary angiogram was negative for pulmonary emboli but identified a 3.2 × 2.5 cm spiculated opacity in the peripheral right lower lobe with extensive mediastinal lymphadenopathy (Fig 1). The patient was afebrile, and his white blood cell count and differential were normal. Because of the malignant appearing adenopathy and lung lesion, a working diagnosis of cancer was pursued. He was stabilized and discharged with home oxygen, outpatient workup (ie, biopsy and positron emission tomography/CT), and follow-up with medical oncology.

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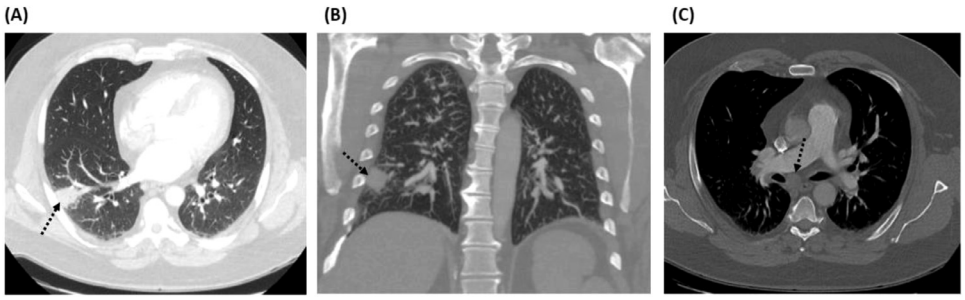

Figure 1 Computed tomography pulmonary angiogram demonstrates a lung mass and mediastinal lymphadenopathy. (A, B) An ovoid mass with irregular margins in the peripheral aspect of the right lower lung. (C) Mediastinal lymphadenopathy (station 7, subcarinal).

Unfortunately, 2 days later, the patient returned to the emergency department with worsening headaches, right-handed discoordination, and paresthesias. Magnetic resonance imaging (MRI) of the brain revealed multiple ring-enhancing lesions with associated vasogenic white matter edema and minimal hemorrhage. Two prominent lesions were noted, including a 1.8 × 1.8 cm lesion in the left frontoparietal cortex and a 1.8 × 2 cm lesion in the right cerebellum. At least 9 additional lesions were also identified. The gradient recalled echo heme sensitive sequence demonstrated hemorrhage within several of the left- and right-sided cerebellar lesions. Lesions also demonstrated restricted diffusion. These were reported as findings typical of brain metastases (Fig 2). Steroids, antiemetics, and analgesics were initiated, and the patient was transferred to a tertiary care center for further management. To complete systemic staging, CT of the abdomen and pelvis was obtained, and the results were unremarkable. CT-guided biopsy of the spiculated right lung mass was performed with 4 ample cores. Pathology showed marked inflammatory reaction, consolidation, and some ill-formed granulomas with no distinct neoplastic process evident. Upon arrival, the patient was afebrile, and his white blood cell count was only mildly elevated at 10.9 K/μL. The neurosurgery, radiation oncology, and medical oncology departments were consulted. Radiation oncology recommended against palliative whole brain radiation therapy until an oncologic diagnosis was established. Pathology slides were sent to an outside expert for a second opinion while ongoing testing for mimickers of metastasis was pursued, including granulomatosis with polyangiitis (Wegner's), small vessel vasculitis, tuberculosis, and other infectious etiologies.

While diagnostic workup was ongoing, the patient's symptoms initially improved with dexamethasone and Keppra. However, on the fourth day of this therapy, the patient's condition rapidly declined with fever (39.9°C), confusion, dizziness, weakness, dysphagia, and dysarthria. Owing to an inability to protect his airway, the patient was intubated and transferred to the neurointensive care unit. His white blood cell count was elevated at 26.9 K/μL with neutrophilic predominance, and blood culture samples were drawn. Ceftriaxone and vancomycin were empirically started. Repeat MRI of the brain was obtained to assess interval changes and evaluate the feasibility of resection or biopsy. MRI revealed a significant increase in the size and number of the ring-enhancing lesions (Fig 3). Fluorodeoxyglucose F18 positron emission tomography/CT revealed hypermetabolic activity in the previously identified right peripheral lung lesion and mediastinal adenopathy, but no other foci of fluorodeoxyglucose activity.

Outside pathologic interpretation was consistent with an infectious etiology, and no malignant cells

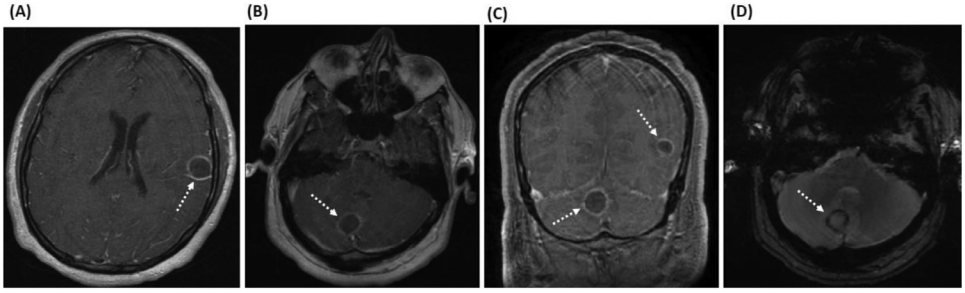

Figure 2 Contrast-enhanced (gadolinium) magnetic resonance imaging demonstrating 2 of the 11 lesions initially present in the brain. (A) Axial views of a supratentorial lesion in the left frontoparietal cortex that measured 1.8 × 1.8 cm. (B) Axial views of a right paramidline cerebellar lesion measuring 1.8 × 2 cm. (C) Coronal view of the right cerebellar lesion and an additional left-sided lesion. (D) Gradient echo sequences demonstrating a small component of hemorrhage within the right cerebellar lesion.

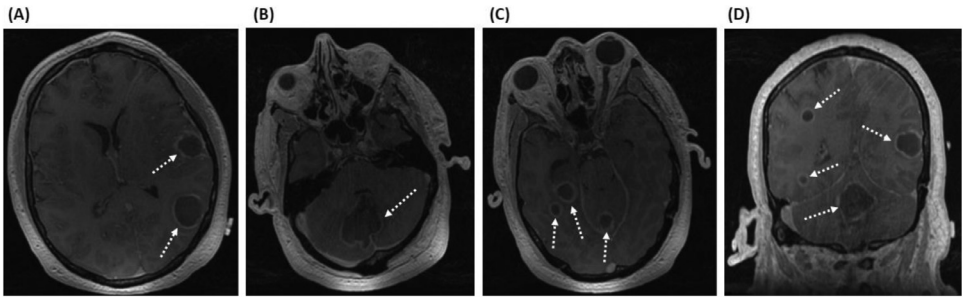

Figure 3 Contrast-enhanced (gadolinium) magnetic resonance imaging performed 9 days after the initial magnetic resonance imaging showing an interval increase in the size and number of lesions after the patient was started on steroids for presumptive brain metastases versus a noncancerous inflammatory condition; workup was ongoing. (A) Axial views of the left frontoparietal cortical lesion showing increase in size to 2.5 × 3.7 cm. Furthermore, a large new lesion was seen posteriorly. There was evidence of local mass effect causing mild entrapment of the temporal horn of the left ventricle. (B) The right cerebellar lesion showing increase in size to 4.5 × 3 cm. (C, D) Axial and coronal views of the right cerebellar lesion with multiple new lesions present throughout the brain.

were identified. The overall histologic features were most compatible with organizing pneumonia with vague granulomas, although an underlying neoplastic process could still be considered given the clinical setting. Blood cultures (2 of 2 sets) tested positive for gram-positive cocci and grew *Streptococcus intermedius.* The infectious disease department was consulted. Further microbiologic workup yielded negative results. Over the next 12 days, the patient made minimal clinical or radiographic improvement while receiving high-dose ceftriaxone.

Owing to the aggressive nature of *Streptococcus intermedius* and minimal radiographic improvement, left-sided temporal, occipital, and parietal craniotomies and surgical evacuation of the largest 3 abscesses was performed. The Gram stain of 2 of the 3 abscess specimens demonstrated 1+ gram-positive branching bacilli with rare *Cutibacterium acnes* grown on 1 of the 3 anaerobic cultures. All fungal, acid fast bacilli, and routine cultures were negative from the 3 abscesses sampled. No malignancy was identified in any of the samples, confirming that the lesions were not due to metastatic disease. Postoperative MRI showed a decrease in the size of the evacuated lesions, with no notable changes in the remaining lesions despite proper antimicrobial therapy.

The patient was successfully extubated, and vancomycin was changed to linezolid to cover possible coinfection with nocardia given the reported Gram stain. Additional workup included transesophageal echocardiogram and maxillofacial CT, both of which were normal. The patient denied any history of intravenous drug use, and HIV testing was negative. The patient was discharged to an acute rehabilitation center for ongoing care, with gradual improvement in his neurologic function. Repeat imaging approximately 3 months after the initial diagnosis showed gradual interval improvement in the size and extent of the brain lesions with resolution of the lung mass, and he remains on intravenous antibiotics at the time of this writing.

Discussion

This case illustrates the clinical and diagnostic challenge of treating patients with brain lesions. Several disease processes may imitate brain tumors. *Streptococcus intermedius* is known to cause both lung and brain abscesses and mimic brain metastases.[6,8,10] The aim of this teaching case is to highlight the potential pitfalls for radiation oncologists being asked to emergently evaluate and treat patients with neurologic changes from brain lesions of unknown etiologies.

The most common diseases capable of causing brain lesions that may be mistaken for malignancy include abscesses, vasculitides, and demyelinating lesions. Other groups have presented cases of abscesses from non-*Streptococcus* species being initially mistaken for malignant brain lesions.[11-13] As with our patient, white blood cell count may be normal on initial presentation in patients with brain abscesses. Jin et al[14] described a case of a young female patient who developed neurologic symptoms in the setting of a peripherally enhancing brain lesion, initially thought to represent a tumor; however, biopsy revealed this mass to be caused by a primary angiitis of the central nervous system. Similarly, a young female patient with an intracranial mass mimicking a brain tumor was instead found to have an angiitis caused by systemic lupus erythematosus.[15] A case report by Turkistania et al[16] demonstrated a patient thought to have a brain tumor after she presented with headaches, vomiting, and a ring-enhancing brain lesion on MRI, but the tumor was determined to be a tumefactive demyelinating lesion caused by multiple sclerosis. Others have reported similar cases of demyelinating diseases causing lesions that imitated brain tumors.[17,18]

Other mimickers of intracranial neoplasms include foreign body-induced granulomatous reactions in those with a history of neurosurgery,[19,20] intracranial tuberculomas from *Mycobacteria tuberculosis*,[21] *Toxoplasmosis*

Table 1 Magnetic resonance imaging findings associated with brain metastasis versus mimicker brain lesions

Typical findings of malignant brain metastasis	Mimicker brain lesions	References
Associated edema confined to white matter and spares the cortex	Mimickers: Edema does not spare the cortex	4,29
Heterogenous lesional appearance	Abscess/demyelination: Homogenous lesional appearance	30
Hypointense capsule not complete (arc) or not present on T2-weighted imaging	Abscess: Complete hypointense capsule (rim) often present on T2-weighted imaging	4,24,30,31
Capsule wall irregular, thickened, or nodular	Abscess: Capsule wall smooth and thin	24,26
Diffusion restriction not present on DWI (tumor dependent)	Abscess/demyelination: Diffusion restriction on DWI	4,25,29,31
Mixed appearance on DWI	Abscess: Hyperintense on DWI	30
Increased rCBV on PWI	Abscess/demyelination: Lower rCBV on PWI	4,29,31
Present at the gray–white junction	Abscess/demyelination: Present in the deep white matter	25,26
More likely to cause mass effect	Abscess/demyelination/angiitis/AVM: Less likely to cause mass effect	25
Single or multiple lesions in the brain	Abscess/demyelination: Multiple lesions throughout the brain	30
Variable rates of growth depending on etiology	Abscess: Usually displays rapid growth over days to weeks	25

Abbreviations: AVM = arteriovenous malformations; DWI = diffusion weighted imaging; PWI = perfusion weighted imaging; rCBV = relative cerebral blood volume.

gondii,[4] and granulomas induced by autoimmune conditions such as sarcoidosis[22] and scleroderma.[23] Less common imitators include neurocysticercosis, syphilitic gummas, invasive mold infections, granulomatosis with polyangiitis, neurocutaneous syndromes, radiation necrosis, cerebral venous thrombosis, arteriovenous malformations, and other rare granulomatous and autoimmune conditions.[4,5,24]

The approach to determining the etiology of brain lesions should begin with careful consideration of radiologic imaging, laboratory test results, patient history, and overall clinical presentation.[4,25,26] The importance of multidisciplinary collaboration cannot be overstated as a means of bringing together various expertise and experience to arrive at a proper diagnosis. If brain lesions are present in the setting of a known primary malignancy, biopsy may be avoided if other etiologies have been satisfactorily ruled out. If there are coexisting lesions that are more safely accessible, as in the case of our patient, these should be biopsied first to establish a diagnosis rather than a more invasive intracranial biopsy.[27] However, a tissue biopsy remains the best way to definitively diagnosis brain tumors and should be performed if the diagnosis is uncertain.[27] Ongoing research is evaluating the role of circulating tumor DNA of the cerebrospinal fluid to diagnose primary and metastatic brain tumors in place of a standard biopsy. This technique is commonly referred to as a liquid biopsy.[28]

Although the diagnosis of brain metastasis on isolated imaging scans should be approached with caution, imaging is a critical component of the noninvasive diagnosis of brain lesions. MRI remains the best modality to characterize intracranial pathology.[25] Table 1 outlines MRI findings associated with metastatic brain tumors compared with potential mimickers. This table serves to illustrate general patterns only. Overlap does occur between groups and is dependent on the etiology of the tumor.

Conclusions

Numerous nonneoplastic pathologies can mimic metastatic brain tumors. In the absence of diagnostic confirmation, radiation oncologists and other oncology providers should be cautious to rule out alternative diagnoses before proceeding with empirical cancer-directed treatments. This is particularly true in urgent clinical situations in which improper treatments could cause significant patient harm.

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