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Teaching Case

Non-Small Cell Lung Cancer With Brain Metastases and Concomitant *Listeria Monocytogenes* Brain Abscesses

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Introduction

Brain metastases are typically treated with surgical resection and/or external beam radiation therapy. Unfortunately, after initial treatment, many patients will develop additional brain metastases. Given the risks associated with neurosurgical procedures and the high likelihood that a new brain lesion represents a metastasis in these patients, pathologic confirmation prior to treatment of each new brain lesion is typically not pursued. Furthermore, omitting pathologic confirmation via biopsy or resection may be favored for many such patients to avoid prolonged suspension of systemic therapy during perioperative preparation and recovery. Nonetheless, one must consider other etiologies of new brain lesions when they appear. Many patients with metastatic cancer are prescribed immunosuppressive medications, such as cancer-directed systemic therapies and/or corticosteroids. Corticosteroids are often prescribed to manage vasogenic edema and its accompanying symptoms associated with brain metastases. As such, it may be reasonable to include infectious etiologies with the development of brain lesions, such as abscesses, which can radiographically appear similar to metastases[1-3] in the differential diagnosis.

Concomitant brain metastases and abscesses are a rare occurrence and challenging to diagnose and treat. In this Teaching Case, we describe our experience of managing a patient with de novo metastatic non-small cell lung cancer to the brain who, shortly after diagnosis and treatment of initial brain metastases, developed new brain lesions that were initially presumed to be new metastases and treated with radiation therapy. However, the lesions rapidly progressed and were ultimately determined to be brain abscesses from *Listeria monocytogenes*. We also summarize the existing literature on this clinical situation and discuss essential components of the decision-making process that may help to identify, treat, and ideally reduce the chance of this dual, morbid clinical situation from happening in the future.

Patient Case

The patient was 52 years old when he presented to the hospital with a cough, vertigo, and headache. Workup eventually revealed large masses in the right upper lobe of the lung and liver. Biopsies of both revealed poorly differentiated adenocarcinoma of the lung, primarily positive for epidermal growth factor receptor (EGFR) mutation

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Research data are stored in an institutional electronic medical record system and will be shared upon request in HIPPA-complaint form.

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(in-frame insertion exon 20 − gain of function) and negative for other mutations and programmed death-ligand 1 tumor proportion score of 90%. Magnetic resonance imaging (MRI) of the brain with/without contrast revealed 8 peripherally enhancing brain lesions with vasogenic edema and restricted diffusion throughout the cerebrum and cerebellum (Fig. 1). The patient was started on dexamethasone 4 mg 3 times daily by mouth with the potential to decrease to 2 times daily pending clinical response. The case was discussed at a multidisciplinary tumor board, where it was felt that the lesions likely represented brain metastases and did not require pathologic confirmation, with a consensus recommendation to treat them with radiation therapy. The patient subsequently underwent single-fraction stereotactic radiosurgery (SRS) to 20 Gy or stereotactic body radiation therapy (SBRT) to 30 Gy in 5 daily fractions to all brain metastases, depending on their size and location, after which a steroid taper titrated to neurologic symptom recurrence was initiated. A prophylactic proton pump inhibitor (PPI) was started. Prophylactic trimethoprim/sulfamethoxazole was started about 1 week after initiation of steroids, at which point the first course of SRS/SBRT had not been started while the diagnosis was being pathologically confirmed and the treatment of the brain metastases (ie, surgery or radiation) was being determined. Moreover, at that point, it was anticipated that the patient would require a prolonged steroid course and taper given the severity of the patient's symptoms and cerebral edema associated with the metastases, and thus prophylactic trimethoprim/sulfamethoxazole was recommended. However, the latter was shortly after transitioned to atovaquone due to elevated liver enzymes.

One month after finishing radiation therapy, the patient remained on steroids, given the recrudescence of neurologic symptoms with tapering. Expanded tumor genomic profiling send-out testing to determine systemic therapy recommendations was not available to review until about 3 weeks after the first SRS/SBRT. Additionally, the patient's specific EGFR mutation (in-frame insertion exon 20 − gain of function) was not detected by our institutional EGFR testing. At that point, he was considered for enrollment in a systemic therapy clinical trial, which required enrollment screening processes, adding additional time to the patient's course prior to initiation of systemic therapy. The enrollment screening testing included an MRI of the brain, which revealed several new brain lesions, the largest being a 2.1-cm irregular, rim-enhancing mass in the left thalamus with vasogenic edema and peripherally restricted diffusion (Fig. 2). The recently radiated brain metastases were similar or decreased in size and with decreased perilesional edema. The consensus multidisciplinary tumor board recommendation was for SRS/SBRT to all new brain lesions, which were felt to be most consistent with metastases and did not require pathologic confirmation. The patient received single-fraction SRS to 20 Gy or SBRT to 30 Gy in 5 daily fractions for all lesions, including the left thalamic lesion, which received 30 Gy in 5 daily fractions (Fig. 3). During this radiation therapy course, the patient experienced increasing generalized weakness, confusion, headache, and vision and speech disturbances, so he went to the hospital after the final radiation therapy session for further evaluation.

On admission, the patient was afebrile, vital signs were within normal limits, and physical exam, including neurologic exam, was unremarkable. Blood tests showed mild

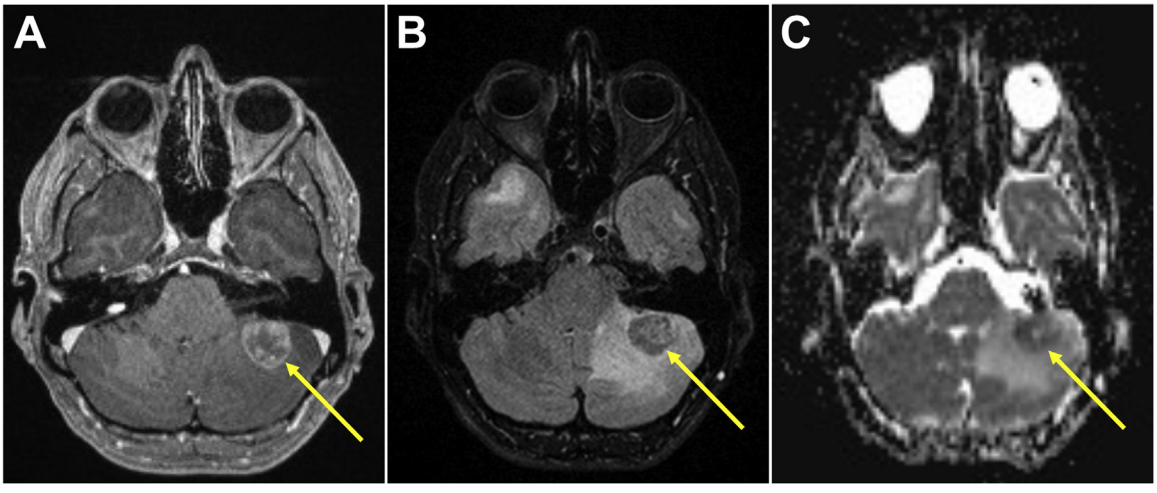

Figure 1 Magnetic resonance imaging of the brain with/without contrast revealing multiple brain metastases discovered at the patient's initial non-small cell lung cancer diagnosis. (A) T1-weighted axial view with contrast of a peripherally enhancing left cerebellar metastasis. (B) Fluid-attenuated inversion recovery (FLAIR) sequence axial view demonstrating vasogenic edema surrounding the left cerebellar metastasis. (C) Diffusion-weighted imaging using the apparent diffusion coefficient demonstrating restricted diffusion of the left cerebellar metastasis.

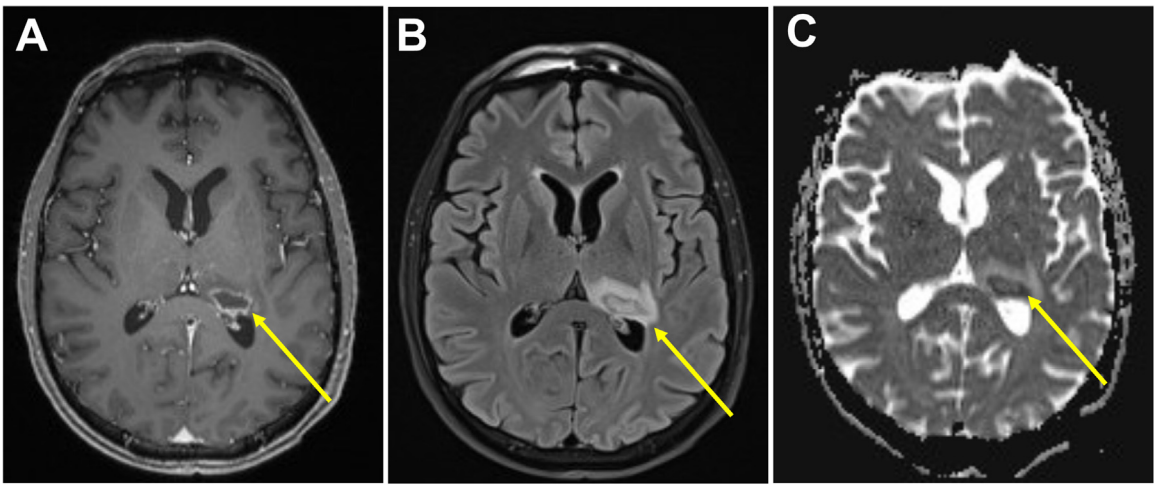

Figure 2 Magnetic resonance imaging of the brain with/without contrast showing the new left thalamic brain lesion after previous radiation therapy to original brain metastases. (A) T1-weighted axial view with contrast of peripherally enhancing new left thalamus lesion. (B) Fluid-attenuated inversion recovery (FLAIR) sequence axial view revealing vasogenic edema surrounding the left thalamus lesion. (C) Diffusion-weighted imaging using the apparent diffusion coefficient demonstrating peripherally restricted diffusion of the left thalamus lesion, similar to the other metastatic lesions.

leukocytosis, mild anemia, and mildly elevated liver enzymes. An MRI of the brain with/without contrast revealed an increase in the size of vasogenic edema associated with the left thalamic lesion, as well as multiple new rim-enhancing lesions in the left temporal stem and posterior insular white matter and extending along the optic radiation (Fig. 4). Blood cultures were obtained on admission as the patient had now been on steroids for 2 months. Two days later, the blood cultures grew *Listeria monocytogenes,* for which intravenous ampicillin and gentamicin were started. At this point, the brain MRI from admission was reviewed at a multidisciplinary tumor board. In this updated clinical context, the rapid radiographic progression and neurofugal pathway extension of the lesions were more supportive of abscesses over metastases. Additionally, magenetic resonance (MR) spectroscopy of the brain was performed and demonstrated a lactate peak, mildly decreased N-acetylaspartate, and a minimally increased choline peak. This pattern is overall suggestive of a necrotic process, such as an abscess, rather than an active neoplasm, though notably, it can also be seen in previously radiated tissue[4] (Fig. 4).

Lumbar puncture was positive for *L monocytogenes* on polymerase chain reaction testing, although cerebrospinal fluid cultures were negative. The patient also underwent stereotactic biopsy and aspiration of the left thalamic and left insular lesions, which on pathology showed necrotic tissue consistent with abscess and no evidence of malignant cells, though Gram stain was negative; however, specimen cultures were positive for *L monocytogenes*. The

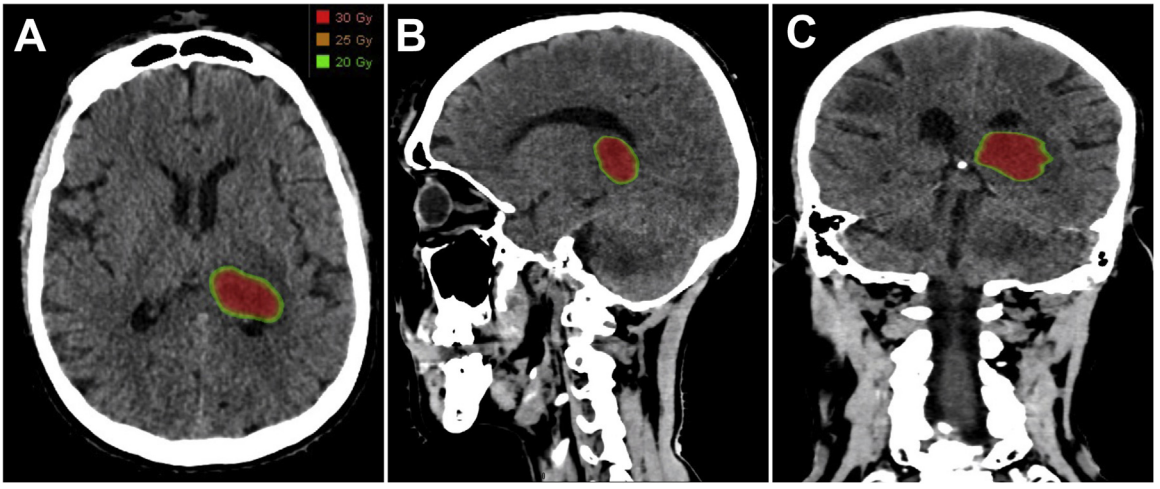

Figure 3 Radiation therapy plan for treatment of the left thalamic lesion in axial (A), sagittal (B), and coronal (C) views on computed tomography simulation scan. This lesion received 30 Gy in 5 daily fractions.

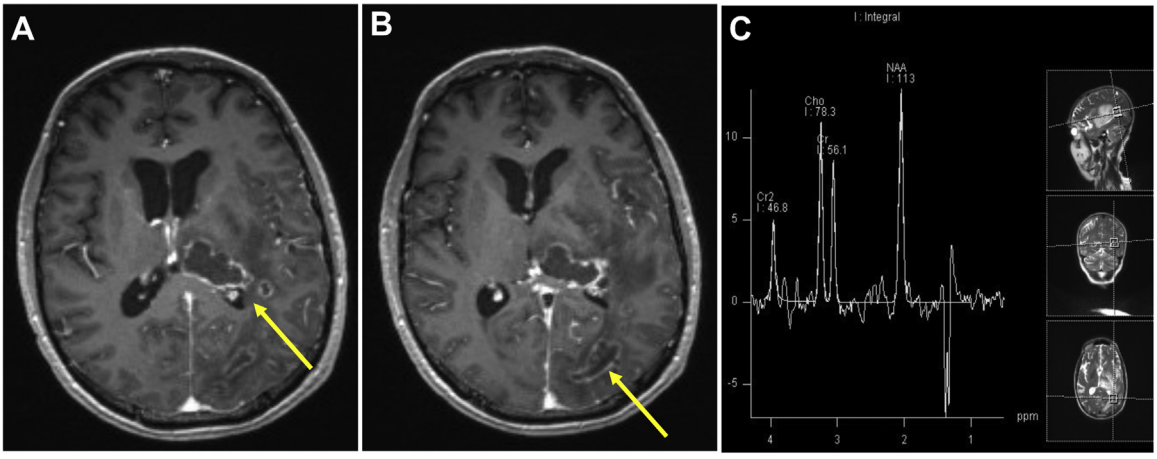

Figure 4 Magnetic resonance imaging of the brain with/without contrast demonstrating an interval increase in the size of the left thalamic lesion on T1-weighted axial view with contrast (A) shortly after completion of radiation therapy. (B) T1-weighted axial view with contrast of a new peripherally enhancing lesion in the left optic radiation that was found after completion of the radiation therapy course for the left thalamic lesion. (C) Magnetic resonance spectroscopy of the left optic radiation lesion demonstrating a lactate peak, mildly decreased N-acetylaspartate, and a minimally increased choline peak, overall suggestive of a necrotic process and unlikely to be an active neoplasm.

patient was continued on intravenous ampicillin alone for 8 weeks, during and after which multiple brain MRIs revealed shrinkage of the abscesses and their associated edema, although without complete resolution (Fig. 5). Systemic therapy initiation was delayed until complete resolution of the brain abscesses. However, at this point, it had been 4 months since diagnosis and without systemic therapy. In an effort to finally start systemic therapy, intravenous ampicillin was resumed with the initiation of systemic therapy in case the *Listeria* infection had not been fully cleared. Shortly after the initiation of systemic therapy, the patient was admitted to the hospital for seizures, at which point an MRI of the brain revealed multiple new brain lesions. These lesions were felt to be more consistent with new metastases rather than abscesses, particularly since the prior abscesses continued

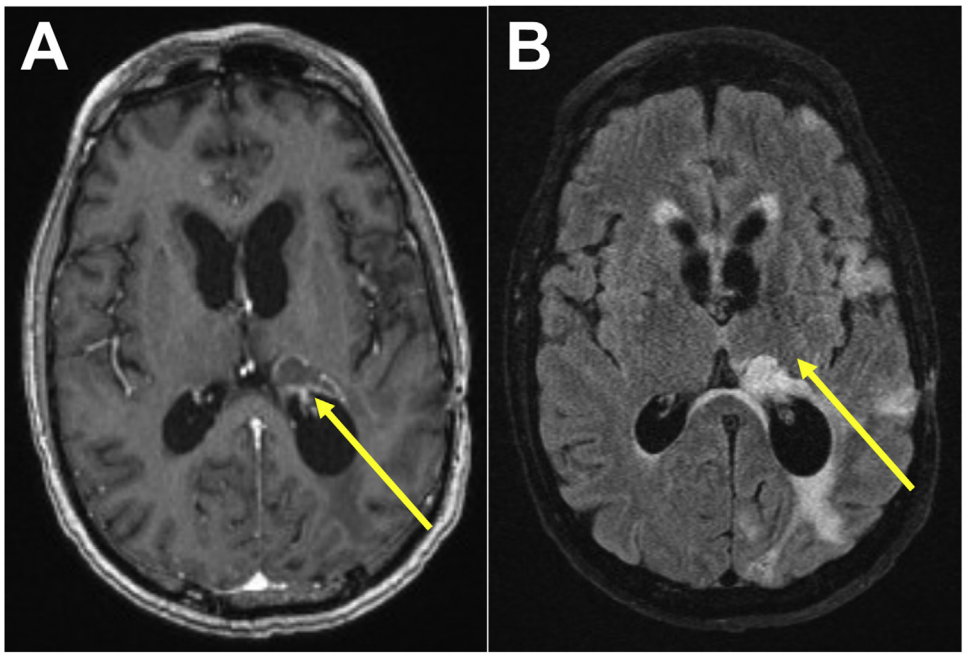

Figure 5 Magnetic resonance imaging of the brain with/without contrast obtained 3 months after diagnosis of brain abscess and intravenous antibiotics. (A) T1-weighted axial view with contrast of persistent but decreased in size left thalamic abscess. (B) Fluid-attenuated inversion recovery (FLAIR) sequence axial view demonstrating resolved vasogenic edema surrounding the left thalamic abscess.

to improve in size. MRI of the brain at that time was also notable for hydrocephalus, possibly from progressive intracranial metastatic disease versus intraventricular dissemination of *Listeria*, for which placement of a shunt was considered but was ultimately not within the patient's goals of care. Intravenous ampicillin was continued on admission. Extracranial imaging was limited at that time, though right upper quadrant ultrasound revealed the progression of liver metastases. The patient was discharged to hospice prior to death, though he remained neurologically altered at the time of discharge, and thus, the ultimate cause of his death may have been neurologic in etiology.

Discussion

Infection with *L monocytogenes* is uncommon, with an annual incidence of 0.6 cases per 100,000 people in the United States.[5] Known predisposing conditions for infection include glucocorticoids,[5] a history of cancer,[6] liver disease,[7] and PPIs,[8] all of which were present in this patient's case. Across the spectrum of clinical manifestations of *Listeria* infection, involvement of the brain with the development of abscesses is infrequent, occurring in about 10% of cases.[9] Concomitant neurolisteriosis with brain abscesses and metastases is thus an exceedingly rare occurrence, making it a challenging diagnosis to recognize and manage.

Owing to the rarity of this combination, to our knowledge, there exist only 4 case reports of patients with *Listeria* brain abscesses and concurrent cancer,[10-12] although in only one, both brain abscesses and metastases were present, and in that case, the abscess was within the metastatic tumor.[13] Brain abscesses of any kind with simultaneous primary, particularly glioblastoma, or secondary brain malignancies have also been documented.[14-18] In many of these cases, the abscesses formed within the tumors themselves. In the current patient's case, the pathology of the brain abscesses did not demonstrate any malignant cells, although the abscess was drained with a needle as opposed to resected, which could miss surrounding tumor or tumor destroyed by the abscess.

Aside from the rarity of this clinical situation, the radiographic similarities between brain metastases and abscesses introduce further complexity. This is true for both patients with pre-existing brain metastases, as in the current patient's case, as well as for patients with a new or suspected diagnosis of cancer without a history of brain metastases presenting with a new intracranial lesion.[1-3,19-23] Both brain tumors and abscesses can present as rim-enhancing lesions with central necrosis and peripheral edema. MRI features such as internal restricted diffusion on diffusion-weighted imaging sequence are more suggestive of abscess than a tumor,[24,25] although this finding may be characteristic but not pathognomonic for brain abscess over a tumor.[26] MR spectroscopy, which was obtained in this case, may have some utility in differentiating brain tumors from abscesses, though only when the abscess has not been treated.[25] Overall, MR spectroscopy is ultimately not the only modality to make this distinction; rather, multiple MR modalities in combination with the clinical presentation help to do so.

In the current case, the brain metastases discovered at initial diagnosis displayed varying signals and enhancement patterns, indicating potential differences in metastatic appearances depending on their anatomical location. Additionally, these lesions did not display internal restricted diffusion nor low T2-weighted signal in their capsules, which are typical abscess features. Most of these initial lesions decreased in size after radiation therapy. Interpretation of the first follow-up brain MRI, which detected the thalamic lesion that was later determined to be an abscess, suffered from framing bias, as it was focused on identifying new metastases. Other diagnostic biases, such as attribution and confirmation bias, certainly played a role as well. In retrospect, the left thalamic lesion, despite its absence of completely homogeneous internal restricted diffusion, had an irregular margin, which is suggestive of an abscess, whereas the other smaller lesions, which presented at the same time, displayed a more rounded shape. It should also be noted that the original metastases displayed some restricted diffusion, making the diffusion-weighted imaging change of the subsequent thalamic lesion inconclusive between metastases and abscesses. The brain MRI performed after the second course of radiation therapy, which included the abscess, revealed an increase in the number and extension of cavitary foci around the left thalamus, with the lesions distributed along the white matter pathways contiguous to the thalamic fibers. These cavities exhibited significantly stronger restricted diffusion compared with the original metastatic lesions discovered at diagnosis, indicative of abscess, and the distribution along white matter tracts is typical of *Listeria* infection.

This case also highlights key clinical considerations regarding corticosteroid use. Tapering should be attempted as soon as clinically feasible to reduce the risk of side effects, and health care team members should remain conscious of their duration and continued necessity. Providers should maintain a high level of suspicion for infection in patients undergoing a prolonged steroid course, even when on prophylactic antibiotics, although these are mainly to prevent *Pneumocystis jirovecii* pneumonia.[27] Relatedly, the most commonly used antibiotic for prophylaxis against *Pneumocystis*, trimethoprim/sulfamethoxazole, has efficacy against *Listeria* infection of the central nervous system (CNS).[28,29] The current patient had to discontinue trimethoprim/sulfamethoxazole due to elevated liver enzymes and was switched to atovaquone, which does not have activity against *Listeria*. In fact, this clinical situation of switching trimethoprim/

sulfamethoxazole to atovaquone with subsequent *Listeria* CNS infection has been described in another case report.[30] Additionally relevant to the current case, PPIs, which are often prescribed prophylactically to patients on steroids, may increase the risk of *Listeria* infection.[8]

Finally, multidisciplinary management is vital in such cases to optimize diagnostic accuracy. Case discussion should ideally include members from medical oncology, radiation oncology, neurosurgery, and (neuro)radiology. Depending on the level of suspicion, input from an infectious disease specialist may also be helpful. Ultimately, taking into consideration the proclivity of non-small cell lung cancer to metastasize to the brain, the challenges with distinguishing brain tumor from abscess, and the inherent risks associated with invasive CNS procedures in patients with known aggressive metastatic cancers, the scenario described herein is statistically improbable enough that we do not feel that clinical practice should be substantially altered to include pathologic confirmation of metastatic disease when its presence is seen radiographically. However, abscess development should remain on the differential diagnosis when patients appear to fail brain metastases-directed therapy early with aggressive progression of a lesion in spite of its treatment.

Conclusions

Synchronous brain metastases and abscesses is a rare and morbid clinical situation. Appropriate ordering and careful review of imaging studies, as well as multidisciplinary discussion, may help to identify such cases, though even then, distinguishing between brain metastases versus abscesses in a timely and safe manner may be difficult. Additionally, given the frequency at which patients with brain metastases are prescribed steroids, providers must remain cognizant of steroid duration in order to minimize the risk of serious infection as a result of their immunosuppressive effect.

Disclosures

None.

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