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Multiple Brain Abscesses Complicated by Enterobacter Cloacae: A Case Report

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Abstract: Brain abscess is a dangerous neurological condition with a high mortality when not treated appropriately. In developing countries the incidence and burden of brain abscess is doubled than developed nations. The challenge of diagnosing this condition early on plays a critical role in its progress towards an advanced burden of the disease. Majority of brain abscess presents as a solitary finding, which makes multiple abscesses an uncommon presentation. There is a wide range of pathogens that can cause pyogenic abscess. However, the association of abscess with opportunistic pathogens from distant sites is much less understood. This report represents only the third reported case involving multiple brain abscesses in the setting of chronic *Enterobacter cloacae* pulmonary infection on an adult male with normal immune status, a unique opportunity in exploring the pathogenic mechanism and clinical process of this condition.

Keywords: brain abscess, Enterobacter cloacae, encephalopathy, neurosurgery

Introduction (Background):
Intracranial brain abscess (BA) remains a life threatening condition in developed and developing countries. It accounts for approximately 8% [1] of all intracranial mass, and while the majority of brain abscess presents as a single focus (76%) [2,3] very few presents with multiple lesions (23%) [2,3]. The findings of headache, fever, seizure, vomiting and focal neurologic deficits are supportive findings but not specific for the condition. The progression of brain abscess can lead to encephalopathy and potential herniation from surrounding cerebral edema and mass effect. This condition is commonly encountered in young males although it can occur in any age group. In developing countries, the incidence in children has been reported to as high as 25%.

The etiology of brain abscess is a key indicator in understanding the pathogenic mechanism involved. In the pathogenesis of brain abscess, the most common mechanism involves direct, contiguous spread from sinusitis, chronic ear infection and dental infection. This mechanism accounts for at least 50% of the cause. In children, dental abscess or carries is a significant cause of pyogenic abscess. The second most common etiology is through hematogenous spread from distant source. Pulmonary infections were the most common cause of brain abscess through hematogenous spread. Chronic pulmonary lung diseases caused by Streptococcus pneumonia [4] and pulmonary hemorrhagic telangiectasia [5] is an important determinant in the development of polymicrobial abscess. Pulmonary lung diseases create an environment of bacteremia which can result in the formation of small infected emboli and enter the arterial circulation in the brain.

In immunocompromised state, pulmonary disease has been strongly correlated with the development of polymicrobial and opportunistic pathogens in brain abscess. Parasitic alveolates, fungal and mycobacterium pathogens have all been associated with disseminated infection and can lead to abscess formation through direct and hematogenous spread. The association of facultative anaerobe and obligate aerobe with brain abscess formation is much less understood which is inherently due to lack of available observation and data. However, the potential for these agents to cause cerebral abscess remains high particularly in immunocompromised state.

Recent advances in diagnostic modalities with the use of brain imaging studies have significantly altered the management and treatment of this CNS infection. Recent large clinical studies [6,7] reveal the complexity in managing this condition due in large part from advanced state of clinical burden by the time

diagnosis is made. Most patients already present with a well formed abscess at the time of presentation [1]. This lead time prior to diagnosis represents an important phase in the development of multiple brain abscesses, which carries a higher mortality rate of 62-100% [8,9].

Brain imaging studies are essential in understanding the morphology of the abscess. The role of conventional MRI studies in pyogenic brain abscess (BA) is critical in discriminating between cystic and solid components. The common MRI findings in BA would reveal hypointense signal in T1W1 and hyperintensity signal in T2WI, with ring-shaped enhancement and extensive surrounding edema [2]. The use of diffusion-weighted MRI allows for the differentiation of abscess against cystic necrotic tumors [10]. The lack of availability of MRI often necessitates the use CT scan which provides for rapid assessment of abscess formation and other accompanying intracranial signs of hydrocephalus, hemorrhage, or acute brain edema. MR spectroscopy has been increasingly used for the evaluation of brain abscess, but experiences are limited. Studies involving in vivo H-MR spectroscopy data analyzing the etiology of brain abscess based on the metabolite markers[11] demonstrate the lack of specificity in differentiating pyogenic abscess especially between obligate anaerobes and some facultative anaerobes.

Case presentation

This was a case of a 32 year old male, previously healthy, who presents with a history of loss of consciousness. The patient was found in his room unconscious but with spontaneous breathing. He remained stupor and lethargic on subsequent attempts to wake him. He was brought to the hospital where he was admitted. His initial GCS score was 10-11.

According to his family, 2 weeks prior to his presentation, he was experiencing general malaise with associated fever, mild headache and non-productive cough. He felt well enough to continue working at the shipbuilding yard where he was employed as electrician. After 1 week, his condition continued to worsen. During daytime he appeared increasingly confused, more irritable and easily agitated, while at night he had difficulty sleeping. His headache worsened and was characterized as diffuse, pressure and sharp, non-throbbing with no associated visual obscurations. He also began to complain of nausea and vomiting which was not always associated with the headache. The patient began to take NSAID's intermittently which afforded mild, temporary relief.

2 days prior to admission, his condition deteriorated markedly. His vomiting became persistent in the setting of intractable headache. His mental status became irregular with periods of agitation, poor attention, and intermittent lack of orientation. More profoundly he was generally more sleepy and lethargic. There was no medical consultation done up to this point.

On the day of admission, he was found to be unresponsive. An initial head CT scan revealed multiple brain abscesses, cerebral edema with no midline shift, and no intraparenchymal hemorrhage and calcifications noted. He was started on cerebral edema protocol (mannitol, dexamethasone) and empiric broad spectrum antibiotic (ceftriaxone). Chest x-ray (Image 1) was notable for right perihilar consolidation. No lumbar puncture was done. A neurology and neurosurgery consult was only obtained after 1 week of hospitalization due to lack of access to clinical specialists. By then, the patient was generally unresponsive and remained lethargic with GCS 9-10. He did not present with cerebral posturing. His dexamethasone and mannitol dosages were adjusted. Blood culture was notable for Streptococcus pneumoniae and Enterobacter cloacae sensitive to levofloxacin, ceftriaxone, and imipenem. Sputum aspirate also revealed Enterobacter cloacae. Subsequently he began to show dramatic improvement. Brain MRI with contrast was also obtained (Image 2) which revealed multiple intraparenchymal brain abscesses.

Following 2 ½ weeks of admission, he began to improve dramatically. He was more awake, coherent and oriented. He had a mild hemiparesis but continued to show marked improvement on his strength and balance.

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His past medical history is remarkable for a chest x-ray done 3 years prior with findings suggestive of right perihilar pneumonia with minimal consolidation. No further management and treatment was done. The rest of his past medical, families, social history were all unremarkable.

Physical exam:

- Vitals: BP: 130/80, HR: 80-90/min; RR: 20's.
- General: lethargic, non verbal.
- Skin: No rash, skin stigmata such as hemangioma, pigmentation, dyspigmentation.
- HEENT: Normocephalic, no dysmorphic features, no conjunctival injection, nares patent, mucous membranes moist, oropharynx clear. Ear drums clear, normal light conus reflexes. Neck: (+) meningismus. No cervical bruit.
- Respiratory: Decrease breath sounds right mid-apical.
- Cardiovascular: Regular rate, normal S1/S2, no murmurs, rubs, or gallops
- Abd: Bowel sounds present, abdomen soft, non-tender, and non-distended. No masses palpable or hepatospleenomegaly.
- Extremities: Warm and well-perfused. No arthralgia. ROM full.

Initial neurologic exam (1 week after admission):

- Mental Status: Lethargic, non-sustainable arousal, non verbal. Localizes to deep pressure stimuli.
- Cranial Nerves: Pupils equal and reactive (5 to 3mm); EOM smooth, limited; few beats nystagmus; optic disc margins dull on funduscopic exam. Corneal reflex brisk. Visual field limited with confrontation test, intact facial sensation (pressure, pinprick), face symmetric. Hearing unable to assess. Gag reflex normal.
- Bulk: Normal muscle bulk; Tone: increase appendicular tone.
- Strength: unable to assess

Reflexes:	Biceps	Triceps	BrachioRad	Patellar	Ankle	
Right	3+	3+	3+	3+	Clonus beats	
Left	3+	3+	3+	3+	Clonus beats	

Plantar responses extensor bilaterally
Sensory: withdraws to touch, deep pressure.
Coordination/Gait: unable to assess.

Discussion:
Brain abscess (BA) is a condition that requires a well planned treatment and management. Most BA formation involves a single lesion and about ¼ of reported cases are multiple lesions. The etiology of BA can be multi-factorial, although the majority of cases involve commonly a contiguous, hematogenous route and traumatic penetrating head injury. The most common aerobic organism often identified is Streptococci among aerobic pathogens, while the most common amongst anaerobic pathogen include Bacteroides fragilis and Peptostreptococcus.

This case represents a unique opportunity in exploring the potential pathogenic mechanism in the development of multiple BA from a facultative anaerobic microorganism, in case Enterobacter cloacae. Reported case(s) of brain abscess complicated by Enterobacter cloacae infection have been rare. Prior to this case, there have been only 2 case reports on BA and Enterobacter cloacae infection, following advanced search on previously published citations. The *first (1^{st})* case reported was a neonatal infection with Enterobacter cloacae in a premature infant [12]. The neonate was being treated with cefotaxim and amikacin before five brain abscesses were discovered. The antibiotic was then switched to axepim and ciprofloxacin with complete regression of cerebral abscesses. The *second (2^{nd})* reported case involved multiple cerebral abscesses on a preterm infant following eneterobacter cloacae sepsis [13]. In both cases

the presentation of multiple cerebral abscesses was complicated by Enterobacter cloacae sepsis. There was no clearly defined pathogenic mechanism reported, though even with current research work the virulence associated properties of this opportunistic pathogen remains unknown. The possibility of nosocomial bloodstream infection as the pathogenic mechanism should be strongly considered in these cases.

The presenting symptoms of brain abscess includes headache, fever, and changes in sensorium [7,14,15] which may occur progressively over a span of 2 weeks. The symptom of headache is dull, often diffuse and non-specific in location. Associated symptoms of nausea, vomiting, focal neurologic signs and presence of seizures may herald the progressive nature of the disease rather than the severity of this condition. The clinical symptoms of our patient started 2 weeks prior to his admission. His initial complaint of fever, headache and general malaise are part of the initial clinical spectrum in BA. The progressive deterioration of his mental status to confusion and lethargy suggests the increased burden of multiple brain abscesses and affected cortical brain involvement. During this period of rapid neurological change, the problems of cerebral edema (inflammation, swelling) [1,7] and mass effect from these multiple intraparenchymal lesions can lead alterations in mental status, which he exhibited 1 week prior to admission. Other findings of focal seizure and weakness are indications of potential vascular compromise or mass effect.

Pulmonary infections including empyema, abscess, and pneumonia may act as sources of infection and spread hematogenous leading to BA formation. The presence of non-productive cough early on in this patient suggests pulmonary disease involvement in the pathogenesis of BA. Hematogenous dissemination is the second most common (25%) etiology and can lead to multiple brain abscesses [16,17] involving the middle cerebral artery distribution areas. The focus of these multiple lesions is often in the chest with poorly encapsulated abscesses and carries a very high mortality rate [18]. The MRI findings of multiple abscesses scattered throughout the frontal, temporal and parietal cortical gray & white matter distribution areas are highly suggestive of anterior and middle cerebral artery territories on our patient. In addition the findings of right perihilar consolidation on chest x-ray provides basis for the likely nidus of infection in our patient. This finding correlates with the research data on Enterobacter cloacae related pulmonary disease which indicates its predilection to perihilar involvement [19,20].

The role of imaging studies is central in the diagnosis and management of CNS infections. Advances in neuroimaging studies have significantly improved the management and outcome of BA infection. The typical finding on CT scan or MRI is a hypodense lesion with a contrast-enhancing ring. While the role of CT scan provides early detection and characterization of the abscess, the MRI in contrast provides accurate characterization of the lesion. Conventional MRI findings reveal high signal intensity on the central area or core of liquefactive necrosis, while the surrounding edematous brain tissue gives low signals on T1-weighted images [21].
The MRI findings (image 2) of irregular mass with central necrosis and surrounding poorly defined areas of edema represents capsule formation which correlates with late stage BA formation. Various studies [21,22] involving the characterization of the enhanced ring sign are largely non-specific in differentiating between fungal infection, tumor or pyogenic abscess. An important distinction, however, can be made between abscess and tumor based on the borders of the lesion. In image 2, there are lesions with poorly defined borders with configuration that extends from the grey to white matter junction areas. Findings of white matter infiltration with thinned grey matter border suggest abscess formation since abscesses tend to grow away from the better-vascularized grey matter [1].

Enterobacter is a genus of a common Gram-negative, facultative anaerobic, rod-shaped, non-spore-forming bacteria belonging to the family *Enterobacteriacae*. *Enterobacter cloacae* (*E. cloacae*) is ubiquitous in terrestrial and aquatic environments (water, sewage, soil, and food). It is primarily transmitted thru respiratory infection, with disease burden leading to brain abscess, septicemia, and disseminated intravascular coagulation as the primary leading causes of its complication. Over the years the emergence of E. cloacae as a nosocomial infection has been well known and have taken on an important role as opportunistic and multiresistant bacterial pathogens for humans. Although much is known in terms of its morphology, the pathogenic mechanisms and factors contributing in the disease associated with the *E.*

cloacae complex are not well understood yet; this could be due to the scarcity and the dispersion of information available [23].

The emergence of antibiotic multi-drug resistance in the treatment of *E. cloacae*, has been an enormous challenge in recent years. Due to its ability to overproduced AmpC beta-lactamase resulting in gene suppression and through its property of transferring ampC gene on plasmids, *E. cloacae* has managed to develop resistance to third-generation cephalosporins [24,25]. In the last decade, *E. cloacae* has emerged as the third most common *Enterobacteriacae* resistant to third generation cephalosporin with enteric *E. coli* and *K. pneumoniae* [26]. Imipenem remains the most effective antibiotic of choice in the treatment of *E. cloacae* infections.

Conclusions

Brain abscess is an important cause of morbidity in neurosurgical cases. It provides a significant challenge to clinician not only in its initial diagnosis, but also in the management and treatment of the disease. The emergence of brain imaging study in the diagnosis cannot be understated as a means to further elucidate and characterized the morphology and patterns of the abscess. The development of functional MR imaging techniques such as MRI (diffusion-weighted imaging, DWI) provides early detection of brain abscess from tumor lesions. Current research in MRI-DWI sequences features recognizable patterns from candidate infectious agents that in the future may serve to help identify the etiologic agent of brain abscess.

The use of antimicrobial agents remains an important treatment modality outside of surgical intervention, particularly in multiple brain abscesses. The emergence of multidrug resistant organism has been a critical factor in managing patients with and without surgical intervention. Enterobacter cloacae (*E. cloacae*) is a ubiquitous, opportunistic microorganism that plays a role in combating drug resistance. Chronic pulmonary infection can serve as a nidus of infection which can potentially lower the immune resistance of an individual and further exacerbate brain abscess lesions or, even possibly, lead to the development of multiple abscess formation.

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