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Case Report

Rare case of intracranial Salmonella enteritidis abscess following glioblastoma resection: Case report and review of the literature

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Abstract

Background: Worldwide, Salmonella enteritidis (SE) is becoming a common cause of gastrointestinal infections by contaminated food products, mainly eggs. Extra-intestinal manifestations such as brain abscess are more commonly associated with Salmonella typhimurium and are rare in adults. We report the clinical features, treatment outcomes and risk factors predisposing our patient to Salmonella enteritidis brain abscess and discuss relevant literature.

Case Description: A 57-year-old-man developed SE subdural empyema, abscess and possible ventriculitis following reoperation for progression of a right temporal glioblastoma. He initially presented with rapidly worsening headaches over a few days, with a wound discharge and associated meningeal signs. An emergent wound washout revealed pus in the epidural, subdural space and resection cavity. An external ventricular drain (EVD) was placed and cultures revealed gram negative rods. Timely intervention, EVD, and antibiotics resulted in complete resolution. Nine cases of Salmonella abscess associated with primary brain tumor have been reported in literature, most frequently caused by SE in association with glioblastoma multiforme (GBM). We describe our management and outcome in addition to discussing neurosurgical literature on the reported cases.

Conclusions: Re-operative tumor surgery has a higher incidence of post-operative infections, with Gram positive cocci being the most common pathogens. Predisposing factors reported for intracranial salmonellosis include compromised immunity, diabetes, HIV, and recent travel. Chronic corticosteroid use, multiple regimens of chemotherapy, and regions of tumor necrosis likely potentiate this rare infection in GBM patients.

Key Words: Glioblastoma, intracranial abscess, salmonella

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INTRODUCTION

Salmonella is a common cause of gastrointestinal infections usually presenting as gastroenteritis, typhoid, or paratyphoid fever. In cases of infection at other sites, it usually produces characteristic localizing clinical features. Most extra-intestinal infections are caused by *S. typhimurium* with non-typhoid salmonella making up between 1.8% and 9.7% of infections.[5,31] They have a bimodal age distribution with one peak

in children and the other in elderly population.[16,25] The organisms are commonly isolated from blood followed by the urinary tract..[23] Other extra-intestinal sites of infection include, bone, cerebrospinal fluid (CSF), sputum, liver, spleen, and intracranial infections.[4,12,19,24,33] Salmonella enteritidis (SE) is the predominant pathogen associated with non-typhoidal salmonella (NTS) serotype in extra-intestinal infections. Central nervous system infections caused by salmonella are extremely rare, with the first proven case reported by Ohlmacher in 1897.[22] Intracranial salmonella can clinically present as meningitis, subdural empyema, epidural empyema, brain abscess, and the association with primary brain tumors is uncommon.[21,26,30]

We report the ninth case in literature, of this rare infection seen in association with a primary brain tumor. A literature review of salmonella intracranial infections and its association with primary brain tumors is discussed, along with the treatment options and outcomes for this rare infection.

CASE REPORT

A 57-year-old-man underwent resection of a right temporal GBM, followed by radiotherapy and 9 cycles of 5-day temozolomide, irinotecan, and bevacizumab. Fifteen months later the tumor recurred in the right occipital lobe and was treated with radiation and multiple rounds of chemotherapy including (etoposide/bevacizumab for 7 months, followed by imatinib / hydroxyurea / bevacizumab for 2 months, then carboplatin/bevacizumab for another 2 months). He developed progressive disease requiring further surgery. His bevacizumab was stopped 6 weeks prior to the craniotomy and tumor resection. There was no problem associated with wound healing following surgery and the sutures were removed in a delayed manner on the 14th post operative day.

About a month after surgery he developed progressively worsening headaches and noticed a serous discharge from his wound, 2 days prior to presenting in the emergency department. There was no preceding head trauma, fever, history of a urinary, or gastrointestinal infection. There were no other associated neurological symptoms. On examination he was afebrile, with meningeal signs and a fluctuant cranial wound. The remainder of his neurological examination was unremarkable. The wound was partially opened in the emergency room, following which a foul smelling purulent discharge was seen.

His routine labs revealed anemia (hemoglobin 8.3 g/dl), neutrophilic leukocyte (total white blood cells 4.03 x 10^9/L; 84%, with a left shift), thrombocytopenia (platelets 71,000/mm^3), and normal electrolytes. A slightly elevated C-reactive protein (CRP) level (1.3 mg/dl, normal value<0.8 mg/dl) was also noted. Renal and liver function tests were normal. A computed tomography (CT) scan of his brain showed a right sided intracranial and subdural fluid collection with diffuse leptomeningeal enhancement, without any evident mass effect or midline shift [Figure 1]. Although a magnetic resonance imaging (MRI) scan would have been more sensitive and specific, we felt the CT scan provided adequate information prior to our emergent surgical intervention.

The patient underwent an emergent re-exploration of his craniotomy and a wound washout. There was immediate egress of pus under pressure with epidural, subdural, and intracavitary involvement. The right occipital ventricular horn was communicating with the surgical cavity and because of the leptomeningeal enhancement on the CT scan, along with the surgical cavity being filled with pus, a ventricular drain was placed for post operative care. The purulent material was sent for diagnostic studies and antibiotic therapy empirically started with meropenem, vancomycin, and metronidazole. Gram stain of the pus revealed gram negative rod-shaped bacteria and culture grew Salmonella group D (*S. enteritidis*). CSF analysis revealed clear fluid, no blood cells, low glucose (2 mg/dl), and low protein (8 mg/dl) with cultures reported negative for the growth of bacteria, and Acid Fast Bacilli (AFB) testing for tuberculosis. The first blood culture grew Salmonella enteritidis, which was sensitive to ampicillin, ceftriaxone, chloramphenicol, and trimethoprim-sulfamethoxazole. However, urine, stool, and CSF cultures were persistently negative. The chest x-ray, abdominal X-ray, and abdominal ultrasound were all unremarkable. The antibiotics were changed to ceftriaxone (2g intravenous q12 hour) on third day after blood culture sensitivity results were obtained and he was treated for with parenteral antibiotics four weeks.

Figure 1: Computerized tomography scan prior to wound washout. The scan reveals mild extra and intracranial fluid collection along the craniotomy with diffuse intracranial leptomeningeal enhancement

RESULTS

Post operative CT scan revealed no significant extracranial or intracranial fluid collection [Figure 2]. With repeat CSF cultures being negative, the patient had a trial closure of his ventriculostomy, which was tolerated well and after a week, the ventricular drain was removed without need for a shunt. MRI scans were done on day 2, one week and one month following surgical evacuation [Figure 3]. Follow-up MRI scans revealed no evidence of hydrocephalus, tumor progression, post operative ischemic changes or of a recurrent collection in the cavity.

DISCUSSION

We searched the MEDLINE database looking for all patients who developed salmonella intracranial abscess associated with primary intracranial tumor. Patients with detailed medical records, including tumor type, common pathogen isolated, treatment method, and clinical outcome were reviewed.

Including our case, we found nine cases of intracranial Salmonella infections in literature.[1,3,7,21,26,28-30] Table 1 lists the details of the reported cases, treatments and outcomes. Intracranial Salmonella infections were most frequently associated with glioblastoma (6 cases), craniopharyngioma (2 cases), and ependymoma, (1 case). The most commonly isolated Salmonella serotype were SE (7 cases), followed by *S. typhi* (2 cases). Eight (8/9) patients received immediate surgical intervention and antibiotics. Of these eight patients reported, one of them died, another patient had incomplete recovery and the others had significant improvement. One patient was treated with antibiotics alone without surgical intervention; he deteriorated and subsequently died.

Salmonella species are gram-negative facultative rod-shaped bacterium and are pathogenic via transmission to humans through the oral route. The common presentations are usually enteric fever, septicemia, and gastroenteritis.[5] Salmonella "food poisoning" is often seen in developing countries where sanitation is poor. It is however seen fairly frequently in developed countries, subsequent to food contamination in manufacturing

Figure 2: Computerized tomography scan following wound washout in the immediate post operative period. There is no significant intracranial or extracranial enhancing fluid collection after surgical intervention

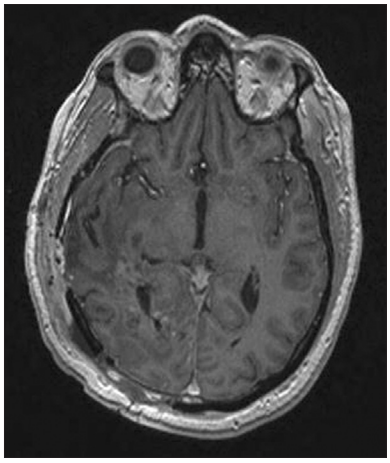

Figure 3: T1-weighted axial magnetic resonance image after wound washout. There is no evidence of fluid collection, hydrocephalus, ischemic changes or tumor progression one month after surgical intervention and antibiotics

Table 1: Summary for all patients with primary cranial tumor associated with intracranial Salmonella

Authors	Age	Sex	Pus C/S	Cranial tumor	Surgical intervention	Outcome
Blazquez D.[1]	2.4	M	Salmonella enteritidis	Ependymoma	yes	Good
Bossi P. H.[3]	57	M	Salmonella D	Glioblastoma	yes	Good
Fiteni I. R. F.[7]	24	M	Salmonella enteritidis	Glioblastoma	yes	Residual hemiparesis
Noguerado A.[21]	78	M	Salmonella enteritidis	Glioblastoma	no	Died
Sarria J. C.[26]	58	F	Salmonella enteritidis	Glioblastoma	yes	Died
Schroder J.[28]	46	F	Salmonella enteritidis	Craniopharyngioma	yes	Good
Shanley D. J.[29]	26	F	Salmonella typhi	Craniopharyngioma	yes	Good
Sharma S.[30]	32	M	Salmonella typhi	Glioblastoma	yes	Good
Our case	49	F	Salmonella enteritidis	Glioblastoma	yes	Good

or food handling by an asymptomatic preparer who is a Salmonella carrier. In the United States, Salmonella species causes an estimated 1.4 million infections and about 400 related deaths annually.[6]

Extra-intestinal infection with salmonella can be classified into 4 groups: primary bacteremia, enterocolitis-associated bacteremia (secondary bacteremia), digestive, and non-digestive local infection.[23] Bacteremia may lead to localized salmonella infections of virtually any organ or tissue. Common sites of involvement are blood and urinary system, less frequently, central nervous system, respiratory tract, bone, joint and liver. Invasive diseases caused by non-typhoid salmonella are usually found in patients with predisposing conditions, although rare descriptions in immunocompetent adults have been reported.[2] Risk factors for invasive disease are related to both host and external factors interfering with natural defense mechanisms against salmonella pathogens. Gastric hypoacidity, bimodal distribution of age, and immune-compromised state including but not restricted to diabetes, malignancy, rheumatologic disorder, HIV infection, chemotherapy, or steroid therapy have been identified as contributive factors in the development of invasive salmonella infection.[13] With the possibility of the infection being nosocomial in origin, the entire treating team was evaluated in detail by infectious diseases, for the presence of a carrier or any other contaminating source and none was found.

Focal post operative intracranial infections are commonly caused by gram positive Streptococci and Staphylococci species, with Salmonella sp. being an extremely rare cause.[18] When Salmonella infections occur, they have a high mortality rate of between 40% and 60%.[5,9] Among Salmonella intracranial infections, meningitis is relatively more common than brain abscess.[19,24] Uncommon presentations like, subdural and epidural abscesses have also been reported.[1,19,24] Brain abscess are more often seen in adults; whereas, meningitis and subdural empyema present more often in children, especially in infants.[19,24] The predisposing factors for intracranial Salmonella include primary or metastatic brain tumors, areas of old ischemia or infarction, subarachnoid hemorrhage, epidural or subdural hematoma, and immunodeficiency.[1,3,7,14,19,21,24,26,28-30] Clinical presentations of brain abscess due to Salmonella have been divided into three groups: 1) brain abscess formation during Salmonella infection elsewhere in the body;[1] 2) abscess formation after recovery from Salmonella infection;[10] 3) abscess formation in patients without any previous history of Salmonella.[26] Our case belongs to this third group, where Salmonella infection was not even suspected. Hematogenous spread of Salmonella is the most frequent mechanism of intracranial spread in glioblastoma, ependymoma, and meningioma. Failure of blood-brain barrier due to tumor invasion and pathological neovascularization, aids the invasion of microbes.[14]

In general, all laboratory examinations, including CRP and WBC, are neither sensitive nor specific for diagnosing a cerebral abscess. A normal CRP and WBC does not exclude the presence of a brain abscess. Meningitis is not a necessary precursor to intracranial Salmonellosis and CSF studies are usually not diagnostic. Moreover, the presence of an intracranial tumor could influence the laboratory results and mask the presence of an infection.[32] In the reported case, laboratory results were of no value even to suspect cerebral infection. The most widely used methods for the diagnosis of a brain abscess include: angiography, radionuclide scans, CT and MRI scans. Of these, CT scan has proved to be the most practical, accurate and offers the best results regarding the location of the lesion, the planning of an appropriate medical therapy and observing the resolution of brain abscess.[8] However, initial CT scans have failed to detect the presence of intracranial abscess and therefore, gadolinium-enhanced MRI studies are very important in detecting underlying intracranial abscesses missed by CT scan.[15] MRI scans are more sensitive and specific in the detection of intracranial abscess, extent of perilesional edema and leptomeningeal involvement.

The management options for intracranial (abscess) are either a combination of surgery and prolonged antibiotic therapy, or medical therapy alone. Nathoo *et al*., have described a management paradigm for supratentorial and infratentorial brain abscesses based on their experience treating 973 cases with varied microbial involvement.[20] The treatment of choice for brain abscesses more than 2.5cms with mass effect and edema, is long-duration antibiotic therapy with surgical drainage.[19,24] In peritumoral or intratumoral abscess, the combination treatment option of surgery with antibiotic therapy (of appropriate duration) is generally sufficient to resolve both the tumor and infection for benign intracranial neoplasms such as meningioma, craniopharyngioma, or pituitary adenoma.[14] For gliomas, further oncotherapy is usually required. Radiotherapy is commonly used in these conditions and may also have antibacterial and anti-inflammatory effects. Chemotherapy, however, is usually not administered, as it compromises patient immunity and may increase the risk of the infection recurrence. In a post operative setting with an associated wound discharge, surgical debridement and intradural exploration is an essential component in the treatment of these patients, irrespective of the size of the underlying abscess or collection.

The non-surgical management of central nervous system (CNS) infections is restricted to patients who are: neurologically intact, unable to undergo surgical procedure and where the organism can be identified from other cultures. In those patients, brain abscesses less than 2.5 cm in diameter, or small subdural empyema without

midline shift and a good response to antibiotics may be successfully treated with prolonged intravenous antibiotic therapy.[2,17]

The choice of antibiotic therapy is complicated by the emergence of resistant strains among Salmonella spp. to ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol, third generation cephalosporins, and fluoroquinolones.[11,31] Furthermore, strains resistant to multiple drugs regimen have been reported.[31] Traditionally, chloramphenicol has been used to treat brain abscesses caused by Salmonella, since the drug is capable of crossing the blood-brain barrier and adequately disseminates through the CNS. However, the fear of toxicity has limited its more widespread use.[24] Third-generation cephalosporins and quinolones have now emerged as alternative antibiotics in the treatment of systemic salmonellosis. Third-generation cephalosporins have excellent CSF penetration and are the most consistently used agents to treat CNS infections caused by Salmonella spp.[24] Fluoroquinolones should be considered a reasonable alternative in infection caused by strains resistant to other antimicrobials since it exhibits excellent *in vitro* activity against most Salmonella strains and penetrates the CSF as well.[27] Ultimately, agents with little resistance and adequate CNS penetration should be continued at least 4 to 6 weeks to treat these complicated infections and to prevent relapses.[19]

CONCLUSION

Focal intracranial infections with Salmonella are rare manifestations of Salmonellosis. First described in 1897, nine cases of intracranial Salmonella associated with primary brain tumor have been published to date. The infection is more frequently associated with immuno-suppressed patients and in our case, the prolonged use of corticosteroids therapy, prior chemotherapies and old age are risk factors contributing to the development of this infection. Early surgical intervention and appropriate antibiotic therapy reduces the mortality and morbidity of this infection.

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