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REVIEW ARTICLE

Gliomas with intratumoral abscess formation: Description of new cases, review of the literature, and the role of ^{99m}TC-Leukoscan

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Abstract Abscess formation within a brain tumor is uncommon. Intrasellar or parasellar tumors are the most common neoplasms that develop such complications. Cerebral gliomas with abscesses are extremely rare. In this paper three rare cases of glioma associated with abscess formation are described. The diagnosis of brain tumor associated with abscess is particularly difficult by conventional neuroradiological studies. ^{99m}Tc-labeled sulesomab can be useful in the diagnosis of brain tumors with intratumoral abscesses. There are no precise guidelines for the diagnosis and treatment of cerebral gliomas associated with abscesses formation for the low number of cases reported to date. Appropriate treatment, aimed at radical surgery, and a suitable antibiotic-protocol, deferring adjuvant postoperative therapy, is associated with a more favorable outcome. A review of the pertinent literature is also performed.

Introduction

Brain abscess are focal and purulent infections of brain parenchyma. They commonly present with seizures, focal neurological deficits, and/or signs of increased intracranial pressure. Brain abscess can be caused by many different types of pathogens, usually bacterial [1,2]. Intraparenchymal abscesses can be secondary to hematogenous dissemination

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of an extracranial site, by direct extension from a contiguous suppurative focus, or secondary to head trauma, neurosurgical procedures, meningitis, or cerebritis [1,2]. In some instances, an etiology cannot be identified [1–3].

Abscess formation within a brain tumor is an uncommon occurrence. The most common brain neoplasms that developed such complications as the result of extension of microbial flora from contiguous infected sinuses are intrasellar or parasellar tumors [4,5]. Cerebral gliomas associated to intratumoral abscess formation are extremely rare.

Despite modern neuroradiological techniques such as magnetic resonance imaging (MRI), MR diffusion-weighted imaging, MR perfusion weighted imaging, and MR spectroscopy (MRS), the preoperative diagnosis of a cerebral glioma associated with an intratumoral abscess remains very complicated [6].

^{99m}Tc-labeled sulesomab (LeukoScan) (Astrim S.n.C., Milano, Italy), a murine immunoglobulin G subclasses 1 (IgG1) monoclonal antibody fragment antigen binding (Fab') fragment, binds the nonspecific cross-reactive antigen-90, an antigen present on the surface of neutrophils, especially the activated ones [7,8]. Recently, Leukoscan has been shown to play a role as a potential diagnostic tool in infectious of various tissues [7–9].

In this study, three unusual cases of glioma associated with abscess formation are presented. All patients had undergone surgery and histopathological examination revealed the presence of a glioblastoma multiforme (GBM) with intratumoral abscess development in two patients and of a diffuse Grade II astrocytoma in one. In all patients a ^{99m}Tc-Leukoscan study was performed. Pertinent literature concerning cerebral gliomas associated with intratumoral abscess formation was also reviewed.

Case reports

Case 1

A 50-year-old woman was admitted, displaying a history of epileptic seizures, fever, and headache for about 1 month. Neurological examination revealed a slight cognitive impairment, aphasia nominum, agraphia, left hearing loss, and mild left facio-brachio-crural hemiparesis. Hoffman and Babinski signs were positive on the left side. She had neck rigidity with a positive Lasègue sign. Laboratory examination demonstrated leukocytosis with neutrophilia and elevated serum level of C-reactive protein. Blood culture was positive for *Staphylococcus aureus* and antibiotic therapy with Vancomycin was given. A brain computed tomography (CT) study demonstrated the presence of an irregularly hypodense mass in the right temporal lobe. Magnetic resonance imaging (MRI) revealed a 3 cm hypointense lesion on relaxation time 1 (T1) weigthed-images and hyperintense on relaxation time 2 (T2) weighted sequences in the right temporo-parietal area (Fig. 1A). After gadolinium was administration a hypointense mass with a peripheral, thickened, enhanced wall, surrounded by a zone of edema, exerting a mass effect on the midline structures was demonstrated (Fig. 1A). MRS showed decreased N-acetylaspartate and creatinine, elevated choline, and a prominent lipid peak which were all indicative of high grade glioma. After some days, the patient underwent another new brain MRI, which documented an additional hypointense mass with a ring enhancement (Fig. 1B). The patient also underwent a ^{99m}Tc-Leukoscan study dual-headed gamma camera (Millennium VG, GE Medical, Chicago, Illinois, USA) equipped with a low-energy high-resolution parallel-hole collimator at 4 hours and 24 hours after tracer administration (555 MBq). Scans were performed by planar (anterior, posterior, and lateral views; magnification 1, matrix 256 $\times$ 256; 900 seconds per frame) and tomographic images (SPET; magnification 1, matrix 128 $\times$ 128; 180° rotation, a 3° step, and shoot technique; 30 seconds per frame at the 1st control and 45 seconds at the 2nd control). Abnormal, intense, and nonhomogeneous uptake of the tracer in the right temporo-parietal region equivalent to MRI findings and consistent with brain abscess was observed (Fig. 1C and 1D). The patient started treatment with steroids for brain edema. Her neurological status gradually improved. However, due to the size of the lesion, and the mass effect on the midline structures, the patient underwent surgery. During the operation a temporal cortical yellow-grayish nodule, vascular, and of soft consistency was noted. In the depth portion the lesion appeared to be a hard-elastic consistency, grayish in color with yellowish fluid purulent in the necrotic areas. It was not possible to collect enough fluid for microbiological examination. Histopathology revealed a GBM with an intratumoral abscess. The patient showed regular postoperative progression, with no additional neurological disorders. The patient died 6 months after surgery for the neoplastic disease.

Case 2

A 47-year-old woman, referred to the Neurosurgical Clinic, Department of Neuroscience with a 2 month history of fever and headache. Neurological examination documented a mild right brachio-crural hemiparesis, lively tendon reflexes in the right upper limbs, Hoffman and Babinski signs were positive on the right side, and right brachio-crural hypoesthesia. Laboratory investigation showed leukocytosis with marked neutrophilia while serum levels of C-reactive protein were normal. Blood culture was positive for *S. aureus* and treatment with a specific antibiotic was started. A brain CT study documented the presence of a large ($>$ 3 cm in size) left hypodense fronto-temporal-parietal hypodense mass. MRI confirmed the presence of a mass in the left temporal lobe. A ^{99m}Tc-Leukoscan study performed as described for the first patient, showed an abnormal tracer uptake in the left temporal region suggesting a brain abscess (Fig. 2A and 2B). Thus the patient was submitted to steroid therapy, with improvement in the neurological status. Nonetheless, due to the mass size, the patient underwent surgery. During surgery it was noted that the arachnoid was significantly thickened and formed a capsule surrounding the lesion. Leakage of a yellowish dense, foul-smelling fluid followed cutting of this capsule. Fluid was aspirated from a cystic lesion, where a neoplastic tissue was found and removed. Formalin fixed and paraffin embedded surgical specimens were submitted for histological examination. The neoplasia underlying the abscess was characterized by moderate cellularity, and it was composed of neoplastic cells showing hyperchromatic nuclei with mild atypia. Intermingled with and hidden by the

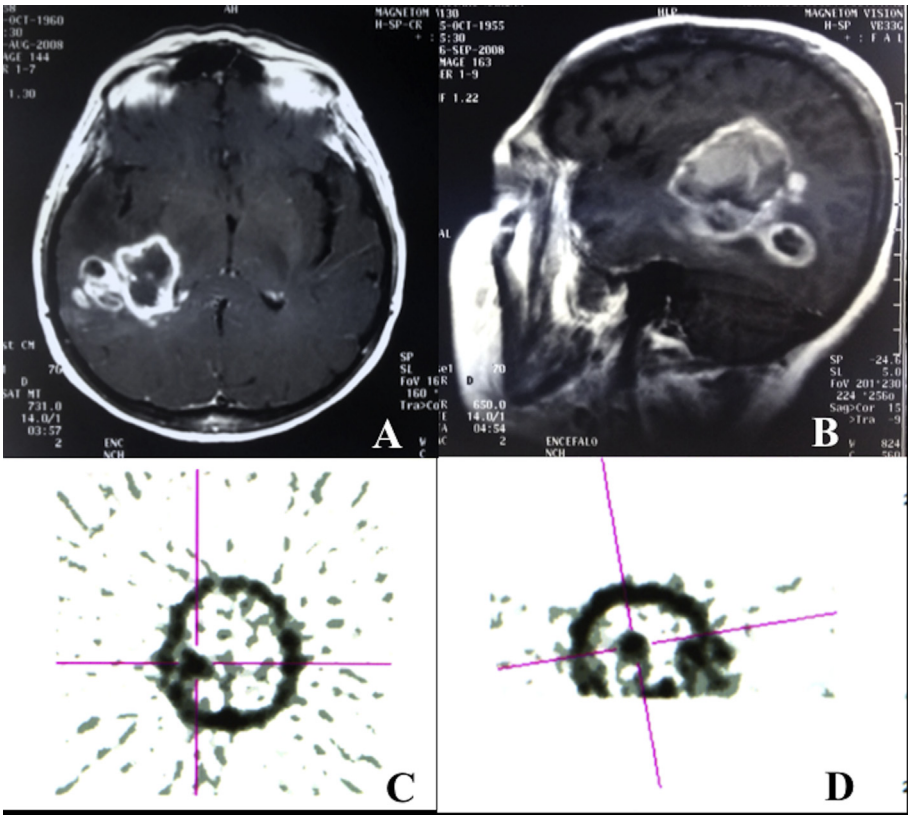

Figure 1. (A) Magnetic resonance imaging (MRI) study shows an irregularly hypointense lesion localized in the right temporo-parietal region. The lesion appears surrounded by a peripheral, thickened, enhanced wall after gadolinium administration. (B) A new MRI study, carried out a few days after ^{99m}Tc-Leukoscan, demonstrates an additional hypointense mass with a ring-like enhancement suggestive for a rapid evolution of the infectious hotbed. (C) Tomographic scans (magnification 1, matrix 128x128; 180° rotation, a 3° step, and shoot technique; 30 seconds per frame): axial sections of the brain. Images show a definite area of abnormal and nonhomogeneous uptake of the tracer in the right temporo-parietal region (red cross-bar) consistent with brain abscess. (D) Tomographic scans (magnification 1, matrix 128x128; 180° rotation, a 3° step and shoot technique; 30 seconds per frame): sagittal sections of the brain. Images show a definite area of abnormal and nonhomogeneous uptake of the tracer in the right temporo-parietal region (red cross-bar) consistent with brain abscess.

inflammatory cells, neoplastic glial cells were found (Fig. 2C). The presence of abundant inflammatory infiltrate composed of neutrophils which permeated the walls of the vessels was detected (Fig. 2D). In the areas of the sample where the inflammatory infiltrate was less evident, the morphological features of the neoplastic cells were apparent. During immunohistochemical analysis the neoplastic cells stained positively for glial fibrillary acid protein (6F2 clone; working dilution 1:50; DakoCytomation, Glostrup, Denmark). A low proliferation index was demonstrated by Ki-67 staining (Ki-67 labeling index: 2%; MIB-1 clone; working dilution 1:50; DakoCytomation, Glostrup, Denmark). On the basis of the histological findings, diffuse fibrillary astrocytoma with abscess formation was diagnosed. Microbiological examination of fluid collections revealed a *S. aureus* infection. The postoperative course was regular with no additional neurological deficits noted. Two months later the patient underwent radiotherapy and is currently alive.

Case 3

A 47-year-old woman was referred to our hospital for weakness in the left limbs, and gait and standing difficulty. Past clinical history was positive for ischemia onset 2 years earlier. Homonymous left side hemianopsia, and a decreasing gradient of left facio-brachio-crural hemiparesis were evidenced. A CT scan and MRI documented the presence of a large (6 cm × 5 cm) oval lesion localized at the right temporal-parietal-occipital undividable with the trigone and occipital horn of the right lateral ventricle area, suggestive for ischemia. After gadolinium administration an intense contrast enhancement of the wall was noticeable. Laboratory investigation was unremarkable except for a mild leukocytosis. About 15 days later a second MRI documented the reduction in size of the known lesion. A total body CT scan revealed a widespread lymphoadenopathy. Thus a bone marrow aspirate was performed, which was negative for lymphoproliferative disorders. All further examinations carried out in the suspicion of an unknown eventual primitive cancer were negative. Another brain MRI was performed 10 days later, and confirmed the presence of a right temporal-parietal-occipital lesion, with significantly higher necrosis and an irregular shape and borders. Also, in this case a ^{99m}Tc-Leukoscan study was performed through the same modalities applied for the other patients. Leukoscan showed an abnormal tracer uptake in the

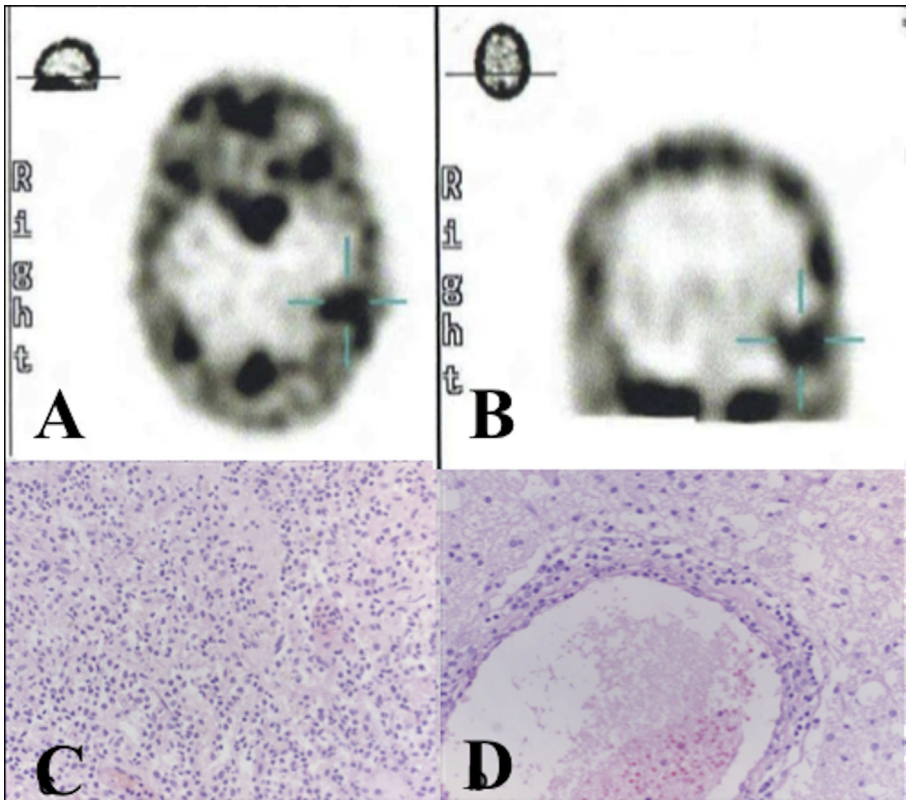

Figure 2. (A, B) Tomographic scans (magnification 1, matrix 128x128; 180° rotation, a 3° step and shoot technique; 30 seconds per frame) obtained 24 hours after intravenous administration of ^{99m}Tc-Leukoscan (555 MBq) using a dual headed gamma camera equipped with low energy high resolution collimator. Axial (A) and coronal (B) sections of the brain: images show a definite area of abnormal uptake of the tracer localized in the left temporal region (blue cross-bar) and consistent with brain abscess. (C) Intermingled with and hidden by the inflammatory cells, neoplastic glial cells were present (hematoxylin and eosin stain; original magnification, ×200). (D) Neutrophils permeating the wall of the blood vessels (hematoxylin and eosin stain; original magnification, ×200).

temporal-parietal-occipital right region corresponding to MRI findings and suggestive for brain abscess. Blood culture was negative and the patient did not have a fever. The patient was treated with antibiotic therapy and underwent a right temporal-parietal-occipital craniotomy for a rapid impairment of hemiparesis. At operation a gelatinous, reddish-gray lesion, with extensive necrosis, pathological vascularization, venous thrombosis, and several pseudocysts filled with a typical glioma liquid were found. In the lateral tumor compartment, a cavity containing a milky fluid was detected and removed. Bioptic samples were sent for both microbiological investigation and histological analysis. The lesion was totally removed and histopathological examination revealed a glioblastoma with abscess formation. No etiologic agent could be found. The neurological state of the patient gradually improved. Two months later the patient underwent radiotherapy; chemotherapy was deferred. The patient is currently alive.

Discussion

Cerebral tumors with intratumoral abscess formation are uncommon. Intrasellar or parasellar tumors are the most common tumor that could develop this unusual event as a direct extension of an inflammatory element from the sinuses [4,5]. Sporadic cases of craniopharyngioma and of meningioma have been also reported [10—12]. Few cases of abscesses within brain metastases have been reported [13]. There is little evidence showing cerebral gliomas associated with intratumoral abscess.

The pathogenesis of brain tumors with abscess formation may be related to multiple factors such as the alteration of the blood—brain barrier (BBB), fenestration of vessels, tumor bleeding, and intratumoral necrosis [14]. Indeed, the failure of the BBB due to tumor invasion and pathological neovascularization, may enable the invasion and permeation of microbes in to the neoplastic tissue. Also, tumor bleeding can take an essential part in the development of an abscess, acting as a culture medium. In addition, high-grade gliomas and GBM often present central necrotic areas which can act a suitable medium for the growth of micro-organisms [15]. Additionally, alteration of the metabolism of neural tissue due to local anoxia resulting from ischemia and venous stasis could be a prerequisite for the abscess formation. Finally, immune defenses may be further suppressed by steroid therapy. All these factors can contribute to the formation of an ideal environment for the settling and growth of bacterial emboli, with possible consequent abscess formation. The immune system plays an important role in resisting bacterial infection. Brain

abscess can be attributed primarily to immunodeficiency and secondarily to various immunosuppressive agents that are used in aggressive cancer treatment or organ transplantation [2]. The hematogenous spread from distant sources such as thrombophlebitis, enteritis, urogenic, dental, and pulmonary infections is the most frequent mechanism of spread for brain tumors.

In the current study a search of the relevant English medical literature published since 1960 to the present time was conducted. The search found 14 eligible cases, the authors, demographic data, grade and location of tumors, pathological agents, probable mechanism of diffusion, and outcomes are reported in Table 1 [6,10,14–24]. From an analysis of the data, a male sex predominance (male/female ratio 1.8:1) was noted; at the time of diagnosis, age ranged from 9 months to 78 years (mean 39.5 years). In six cases the tumor was a GBM, in three cases a low-grade astrocytoma, in three cases the lesion was an ependymomas, and in two cases a high-grade glioma. Prevalent location of the lesion was the temporal lobe (4 cases) and the posterior cranial fossa (4 cases). The most common identified organism (5 cases) was *Staphylococcus*, while in two cases *Salmonella* was revealed. In the remaining cases *Pseudomonas aeruginosa*, *Enterobacter*, and Gram negative bacilli were identified. The etiologic agent was not identified in two cases. Eight patients died while six showed a favorable outcome. The current study shows findings similar to those found in the literature, with the only exception being that in the current study all cases were female. An analysis of total reported cases highlights the high number of malignant gliomas, particularly GBM. This result seems to confirm a possible mechanism of abscess formation in gliomas that are characterized by large necrotic areas and hemorrhages foci.

The differential diagnosis of a brain lesion that shows a ring-like enhancement pattern on CT scan and MRI may be difficult and typically includes necrotic tumor, cystic metastases, and brain abscess [25,26]. Neuroradiological imaging does not have absolute specificity. CT and MRI studies show a role in revealing sudden increases in size of the lesion and atypical perifocal edema. In addition, diffusion weighted imaging (DWI), as well as MRS has recently been shown to be promising tools for the differentiation of ring-enhancement lesions [25]. In the current study MRS showed decreased N-acetylaspartate and creatine peaks, elevated choline peaks, and a prominent lipid peak, which were all consistent for high grade glioma. However, Tsai et al [6] confirmed that DWI and MRS could not differentiate brain tumor and abscess or coexisting tumor with abscess preoperatively.

Nuclear medicine plays an important role in the diagnosis of a multitude of infections, and radiolabelled autologous leucocytes represent the optimal technique for the nuclear medicine imaging of infections [27]. However, this procedure requires a direct handling of blood products, and special training. Intact murine antibodies represent a valid and simple alternative. They are easy to handle and show rapid results, with high sensitivity and specificity [8]. The major disadvantage in this technique is represented by the development of human antimouse antibodies which can cause serious allergic reactions. A valid option to overcome this limit is the use of antibody fragments instead of intact IgG. Various studies which have adopted ^{99m}Tc-labelled monoclonal antibody fragments (^{99m}Tc-Fab′ fragments, sulesomab) to image infection in specific groups of patients have reported a high degree of sensitivity and specificity [8,28]. The small size of the Fab' fragments (50 kD) means that fast imaging is possible, as early as 1–4 hours post injection, due to rapid uptake into the lesion and a lower degree of background activity, and results in excellent imaging quality. Leukoscan localizes the inflammation site through nonspecific extravasation via increased vascular permeability with secondary attachment to post migratory leukocytes already present at the site of infection [7]. Since Leukoscan is an antibody fragment, its blood clearance is fast, with preferential accumulation in infected areas and tiny immunogenicity for low doses [29]. Moreover, this technique is not invasive and has no pharmacodynamic effects.

Immunoscintigraphy with ^{99m}Tc-Sulesomab has been used in various clinical settings to detect infectious foci, including bone, joint and soft tissues, gastrointestinal, and cardiac infections as well as for the investigation of fever of unknown origin [7–9]. The specificity of ^{99m}Tc-Sulesomab in the diagnosis of infectious diseases ranges from 76% to 100% [29]. In addition Gratz et al [7,8] reported an overall sensitivity and specificity of 76% and 84%, respectively, of Leukoscan scintigraphy for the diagnosis of infections involving bone, arthroplastic joint, or other tissues in 138 patients. Similar results were achieved by Cascio et al [30] in patients affected by brucellar spondylitis; the low sensitivity (27.2%) of Leukoscan in these patients was correlated with the chronic phase of the disease.

In brain infectious diseases, labeled leukocyte scintigraphy seems to be able to differentiate infectious from noninfectious lesions. Positive findings indicate that the origin of the brain lesion is almost certainly infectious [27]. However, false-negative results in patients receiving high-dose steroids and weak uptake in brain tumors have been reported [27]. In order to clarify the diagnosis and to design a correct preoperative plan for patients in the current study ^{99m}Tc-Leukoscan was performed. MRI and MRS studies were unconvincing while the results of the leukocyte scintigraphy were successively confirmed by histopathological examination, which also showed the presence of brain abscess. Thus in the current study the sensitivity and the positive predictive value of granulocyte scintigraphy were both 100%. It was noted that the tracer uptake intensity was higher in the second phase. These findings may help differentiate between a brain abscess and a brain tumor, since in brain tumors the tracer uptake intensity is stable throughout the imaging phase. Nonetheless, in the suspicion of a brain abscess, the Leukoscan should be performed prior to steroid and antibiotic therapy which may determine a significant reduction in the tracer uptake.

An intratumoral abscess is considered a life-threatening condition. Differential diagnosis of ring enhancing cystic mass lesions includes primary and secondary brain tumors, mainly cystic glioblastomas, metastases, nonneoplastic cysts, and brain abscesses [25,26]. Early diagnosis of a brain abscess associated to a brain tumor is very difficult. A complete neuroradiological plan also integrated with nuclear medicine imaging techniques and assessment of the patient's history may reduce eventual diagnostic mistakes.

Table 1 Summary of clinical data for each of the reported cases of glioma associated with abscess formation.

Author	Age/Sex	Tumor grade	Tumor location	Organism	Mechanism of spread	Outcome after treatment
Sharma	32 y/M	High-grade glioma	Left temporal lobe	*Salmonella typhi*	Bacteremia	Favorable
Noguerado	78 y/M	High-grade glioma	Left occipital lobe	*Staphylococcus aureus*	Bacteremia	Died
Ichikawa	46 y/F	Glioblastoma	Left frontal lobe	*Staphylococcus aureus*	Bacteremia	Died 8 months later
Nassar	32 y/M	Ependymoma	Fourth ventricle	Not identified	Meningitis	Died 24 hours later
Sarria	58 y/F	Glioblastoma	Left frontal lobe	*Salmonella enteritidis*	Bacteriemia	Died 52 days later
Bansal	11 y/F	Low-grade astrocytoma	Right parieto-occipital lobe	*Pseudomonas aeruginosa*	Bacteremia	Died 3 hours later
Mohindra	35 y/F	Low-grade astrocytoma	Posterior cranial fossa	Not identified		Favorable
	9 m/M	Ependymoma	Posterior cranial fossa	*Enterobacter aerogenes*	Bacteremia	Died 28 days later
Shankar	4 y/M	Ependymoma	Posterior cranial fossa	Not identified	Meningitis	Favorable
Kalita	57 y/F	Glioblastoma	Left occipital lobe	*Staphylococcus aureus*	Bacteremia	Favorable
Tsai	52 y/M	Grade II astrocytoma	Left temporal lobe	*Staphylococcus aureus*	Bacteremia	Favorable
Jho	53 y/M	Glioblastoma	Left temporal lobe	*Staphylococcus Acinetobacter lwofii* Propionibacterium	Bacteriemia	Died 2 years later
Tsugu	45 y/M	Glioblastoma	Right temporal lobe	Gram-negative bacilli	Bacteremia	Died 21 months later
Singh	50 y/M	Glioblastoma	Right fronto-parietal lobe	Gram-negative bacilli	Bacteremia	Favorable
Our cases	50 y/F	Glioblastoma	Right temporo-parietal lobe	*Staphylococcus aureus*	Bacteriemia	Died 6 months later
	47 y/F	Astrocytoma	Left temporal lobe	*Staphylococcus aureus*	Bacteriemia	Favorable
	47 y/F	Glioblastoma	Right temporo-parieto-occipital lobe	Not identified		Favorable

The possibility of intratumoral abscess development should be kept in mind for the immunocompromised or in those patients with an intracranial neoplasm who have a history of extracranial infection or show deterioration of neurological status after an infection. The preferable treatment is surgery with resolution of both the tumor and intracranial infection. A targeted antibiotic therapy of an appropriate duration is mandatory. The current data seem to indicate the value of ^{99m}Tc-Sulesomab, in association with DWI and MRS, for the early diagnosis of brain abscess within brain gliomas. If ^{99m}Tc-Sulesomab is performed prior to drug treatment (particularly steroid therapy), a negative exam rules out infection with a high degree of certainty (high negative predictive value), while a positive result allows a precocious antibiotic protocol with amelioration of clinical signs correlated to brain infection. Therefore, a complete diagnostic definition associated with a correct pharmacologic plan and an aggressive resection can be related to an optimal outcome.

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