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UNIQUE CASE OF MULTIPLE EXTRA-CRANIAL METASTASIS (7SITES) FROM GLIOSARCOMA: REVIEW OF LITERATURE WITH EMPHASIS ON DIFFERENTIATION FROM GBM IN MOLECULAR, HISTOPATHOLOGICAL AND RADIOLOGICAL FEATURES.

Oncology

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ABSTRACT

Gliosarcoma is a highly aggressive but a rare central nervous system neoplasm with a very poor prognosis. Extra-cranial or extra-neural metastases outside the CNS are exceptionally rare events reported to occur in only 0.2–2 % of all GBM. The invasion of dura and extra-cranial metastasis is slightly more common in gliosarcoma than GBM.Herein we report the case of a 60 yr old female with a temporal lobe gliosarcoma with controlled intracranial disease but with extensive extra-cranial metastasis to multiple sites including pleura, lung, liver, gall bladder, adrenal gland, thyroid gland and bones along with deep vein thrombosis.To our belief this is the first case report showing gall bladder and thyroid metastasis from a gliosarcoma. We correlate the MRI, histo-pathologic, immuno-histochemical findings in this rare case and review previous literature reports. We also discuss mechanisms of metastasis from Gliosarcoma along with various features which distinguish Gliosarcoma from Glioblastoma multiforme.

KEYWORDS

INTRODUCTION

Gliosarcoma (GS) is a rare primary malignant tumor of central nervous system accounting for 2% to 8% of all glioblastoma multiforme (GBM) and 0.48% of all intracranial tumors. (1)It has a biphasic morphological pattern with both glial and malignant mesenchymal components. It usually affectsin forth to sixth decade of life (average age of onset is 54 years) with slight male preponderance (males being affected twice as often as females). (2)Therapeutic modalities are surgical resection, external beam radiotherapy and chemotherapy but prognosis remains poor in terms of survival. Historical data showed that the median survival time of GSM is 6 months to 14.8 months, despite multidisciplinary treatment with extensive surgical resection and adjuvant therapies, such as molecular-targeted therapies. (1)

Case history

A 61 yr old hypertensive, non-diabetic female with past history of hysterectomy presented in April 2018 with complaints of gradually progressive left sided hemiparesis initially involving the upper limb and then progressing to the lower limb since 15 days duration. She also gave history of intermittent headache since 5-6 years, irrelevant speech, altered sensorium and a sense of confiding in one's own self of 1month duration. MRI Brainwith contrast revealed a lobulated space occupying lesion involving the right temporal lobe and adjacent right capsule – ganglionic region, measuring approximately 40 x 50 x 60 mm (TR x AP x CC) in maximum dimension with surrounding marked perilesional edema. The lesion showed heterogeneously hyperintense signals on T2W images and iso to hypointense signals on T1W. The lesion had areas of restriction diffusion on DWI images. The lesion showed mildly irregular peripheral enhancement with central non enhancing area. There was mass effect in the form of effacement of right lateral ventricle, 3rd ventricle and midline shift towards left side by 9 mm. There was also mass effect on the ipsilateral cerebral peduncle with displacement towards left. (Figure 1) She was suspected as a case of Glioblastoma multiforme right temporal lobe. She then underwent Right Temporal Craniotomy and Excision of Right Temporal Mass.

Histopathology showed a malignant astrocytic tumour with marked pleomorphism, necrosis, microvascular proliferation & prominent mitosis, scattered giant cells, with focal areas showing spindle cells in fascicular pattern.(Figure 2,3,4,6) IHC showed GFAP (GA-5) positivity in glial component & negativity in sarcomatous component, Vimentin (V9) diffusely positive, p53 (DO7) Positive, Ki-67 (MIB-1) 40%. So, a final diagnosis of Gliosarcoma, NOS (WHO grade IV) was made. MGMT methylation by PCR was positive. IDH1 and IDH2 mutation were negative.

Post op MRI brain with contrast showed a post -operative cavity in right temporal region with mural foci of haemorrhage, surrounding white matter edema in right fronto-temporo-parietal region and few nodular as well as linear foci of enhancement along the walls of the cavity. She received external radiation to Right Temporal region with IMRT technique to a dose of 60Gy/30 fractions along with concurrent chemotherapy with Cap Temozolomide 120 mg during the radiation treatment.

She presented one month later to an outside hospital with complaints of altered sensorium of 2 days duration with cough and respiratory distress of 1 day duration. She was suspected to have? Aspiration pneumonitis with hypernatremia. HRCT chest showed infiltrates. Pulmonology consultation was done in view of B/L pulmonary infiltrates with wheeze and intermittent need for NIV and she was managed symptomatically. USG abdomen was normal. NCCT head was s/o? Post radiation necrosis with ventriculomegaly. So, she underwent therapeutic lumbar Drainage followed by right medium pressure VP shunt placement. Patient tolerated her surgery well and there was slow and gradual improvement in her neurological status. She improved gradually and received 3 cycles of adjuvant Temozolamide .MRI brain with contrast after 3 months of completion of concurrent chemo-radiotherapy showed minimal reduction in the nodular lesion along the postoperative cavity and reduction of enhancement along the posterior margin of cavity. She then received 1 more cycle of adjuvant TMZ.

A few days later, she presented in emergency in our hospital with complaints of cough, breathlessness and right sided chest pain of few days duration one month later. Chest x ray done outside showed large right lung opacity. She was started on broad spectrum antibiotics, oxygen support and other supportive measures.

She underwent a Whole body PET CT with contrast (Dec 2018) which revealed no evidence of disease recurrence at post-surgical, post radiated site. VP shunt was seen in situ connecting left lateral ventricle to peritoneal cavity. FDG avid (SUV max: 18.6) large heterogeneously enhancing centrally necrotic pleural-based soft tissue density mass lesion measuring $8.9_{(AP)}$ x $10.8_{(TR)}$ x $10.9_{(CC)}$ cm was seen in right lung

upper lobe, occupying predominantly the superior segment extending inferiorly into the basal segments and minor transfissural extension into the right upper lobe and middle lobe, another FDG avid (SUV max: 10.4) heterogeneously enhancing centrally necrotic soft tissue density pleural-based mass lesion measuring 5.8 x 3.5 cm was seen in left lingula, and multiple FDG avid pleural-based mass lesions and sub pleural nodules were seen in costal and mediastinal pleura surrounding the basal segments of right lower lobe, largest measuring 6.2 x 3.1 cm (SUV max: 16.8) in lateral basal segment. Few non FDG avid fissural nodules were seen in major fissure of right lung. She also had an FDG avid (SUV max: 4.3) parenchymal soft tissue nodule measuring 1.5 x 1.2 cm seen in the apico-posterior segment of left upper lobe and another parenchymal soft tissue nodule measuring approximately 1.5 x 1.3 cm is seen in the superior segment of left lung lower lobe. There was no evidence of pleural effusion, no mediastinal / hilar lymphadenopathy. Two FDG avid ill-defined heterogeneously enhancing sub-capsular lesions measuring were seen in segment III (1.7 x 1.6 cm, SUV max: 5.9) and segment VIII (1.5 x 1.4 cm, SUV max: 4.8) of liver. Gall bladder showed an FDG avid (SUV max: 6.9) heterogeneously enhancing irregular growth measuring 2.5 x 1.6 cm arising from anterior wall of body of gallbladder projecting into the lumen. Bilateral adrenals were mildly bulky with mildly increased FDG uptake (SUV max: 3.8 on left, SUV max: 3.4 on right). FDG avid subtle lytic-sclerotic lesions were seen in body of C3 and L2 (SUV max: 7.6) vertebra.Metabolically active bilateral hypo dense thyroid nodules were also present. (Fig 7,8)

USG Doppler both lower limbs showed echogenic thrombus in left popliteal vein, posterior tibial vein and anterior tibial vein. CT guided lung biopsy showed a malignant mesenchymal tumor composed of spindle cells having moderate eosinophilic cytoplasm and moderate to markedly pleomorphic hyperchromatic nucleus. Mitotic activity was brisk. Necrosis was abundant. CK Negative, GFAP Negative, Vimentin (V9) Positive, Desmin Negative, SMA Negative, CD34 Negative, S-100 Negative, CD99 Positive and Calratenin was negative. So, a diagnosis of metastasis from sarcomatous component of gliosarcoma was made. (Figure 5)

She was advised chemotherapy but patient refused for any further treatment and opted only for home based palliative care. In conclusion, this is an unusual case of primary gliosarcoma with stable brain lesions but extensive systemic metastases to the lungs, pleura, liver, gall bladder, adrenal glands, thyroid, and bones as well as with deep vein thrombosis.

DISCUSSION

Gliosarcoma (GSM) is a rare but distinct clinic-pathological entity in the classification of central nervous system tumors and constitutes approximately 2% of all the malignant glial neoplasms. (3)It was first described in 1895 by Heinrich Stroebe and was re-described by Feigin in 1955(4)and Robinstein a year later.(5)According to the 2016 World Health Organization classification it is a biphasic tumour, with alternating areas displaying glial and mesenchymal differentiation, it is considered a grade IV tumour and a subtype of GBM IDH-wild type. (6)

Gliosarcoma comprise 1.8–8% of glioblastoma multiforme and are clinically similar to them, affecting adults in the fourth and sixth decades of life, with a higher proportion found in males. (7, 8). Primary spinal Gliosarcomas are rare and affect younger age group. (9)Most GS are de novo, and are hence termed primary GS, whereas those detected at subsequent surgery for previously resected and irradiated GBM are termed secondary gliosarcoma SGS. Secondary gliosarcoma after treatment of primary glioblastoma multiforme and radiation-induced gliosarcoma are exceedingly rare.

The symptoms of this disease may vary according to the location of the tumor. The most common signs include the following: Recurring headaches, vomiting, unsteadiness, vision loss, cognitive problems, seizures, and personality changes. The most common tumor location is the temporal lobe (38.5%), followed by the frontal (23.1%) and parietal lobes (15.4%).

GSM, WHO grade IV tumor, is a bimorphic tumor, containing both gliomatous and mesenchymal regions. The sarcomatous region consists of neoplastic mesenchymal cells with associated reticulin formation. These cells are spindle shaped, and demonstrate nuclear atypia, increased mitotic activity and necrosis. The glial regions in gliosarcoma are typical of glioblastoma, with a varying degree of anaplasia and GFAP expression. GFAP immunostaining is most important in distinguishing between GSM and GBM, with GFAP being present in glial regions, but found in only very low quantities in sarcomatous regions. Vimentin is a marker of mesenchymal cells, with strong vimentin staining in sarcomatous areas but almost no staining in glial regions. It was seen in our case as well. (10)

There has been a lot of debate on the histogenesis of GSM. Feigin and Gross, described GSM as a “collision tumor “and suggested that the cell of origin arises from neoplastic transformation of blood vessels in a pre-existing GBM. But IHC studies could not detect endothelial markers in the sarcomatous component. Some studies suggestits origin from histiocytes, others from fibroblasts, pluripotent mesenchymal cells of the perivascular adventitia, or perivascular spaces. (10)Malignant astrocytes constitute the majority of the glial component in gliosarcomas; however, oligodendroglial components have also been described. Typically sarcomatous components resemble fibrosarcoma or malignant fibrous histiocytoma.(3)Because of the occurrence of similar genetic alterations in both glial and mesenchymal components some people suggest monoclonal origin of the metaplastic mesenchymal differentiation from the astrocytic component.Also, the presence of identical p53 mutations and similar chromosomal imbalances and cytogenetic alterations in both gliomatous and sarcomatous components strongly supports the concept of a monoclonal origin of GSM. (10)GSM have a similar cytogenetic profile to primary GBM with the exception of epidermal growth factor receptor (EGFR) amplification which is rare in gliosarcomas, while EGFR is overexpressed in about 50% of GBM cases . (11)

On computed tomography (CT), the lesions can appear with large necrotic areas and heterogenous contrast enhancement, similar to that of GBMs, or as hyper dense lesions with well-defined margins and homogenous enhancement, and may confuse with meningioma. MR imaging show GSM as a supratentorial tumor with solid and cystic components that is usually peripheral to and invasive of the dura or falx. Frequently a sharply defined lesion with mild-to-moderate peri-tumoral edema, the tumor is generally hypointense to white matter on T1-weighted images and hyperintense on T2-weighted images. After the administration of contrast medium, the tumors are homogeneous orinhomogeneous with intensified peripheral enhancement.Some demonstrate irregular ring enhancement. The enhancement portion of gliosarcoma is less intense on T2-weighted imagesdue to the dense cellularity and fibrous nature ofthis non-glial tissue.Areasof hyperintensity onT2-weighted images represent the gliomatous componentwith associated necrotic or cystic changes.(12)

MR Angiography shows a mixed dural and pial supply in this part of the tumor. The gliosarcomas showed heterogenous enhancement on contrast weighted T1 weighted images. Thick walls and rim or ring like enhancement is likely caused by peripheral displacement of vessels as the tumor enlarges. Intratumoral strip enhancement on enhanced T1 weighted images is another feature due to tumoral angiogenesis and proliferation.(12)

The survival for patients with GSM is equally poor as for those with GBM.(10)Although extra-cranial metastasis from GBM is rare, gliosarcomas are well-known for their systemic dissemination. Extracranial metastases from glioblastoma have been reported in 0.2–1.2% of cases versus 11% for gliosarcoma(13) but it may be as high as 15% in some studies (10)The most common sites are the lungs, liver, and lymph nodes, and there are reports of metastatic foci in the spleen, adrenal glands, kidneys, oral mucosa, skin, bone marrow, skull, ribs, and spine.(14,15,16,17,18,19)Patients with metastases to the neck and liver showed a better prognosis than those with lung metastases. (13) Our patient had 7 sites of metastasis including gall bladder and thyroid which is not reported before.

The reported metastatic foci are constituted by biphasic elements or exclusively by sarcomatous component which points to the sarcomatous component as the potential metastatic source by haematogenous spreading (as seen in our case also) and corroborates the premise that GSM is a distinct entity from GBM. (3)

The intrinsic biological barriers to prevent systemic metastases from the brain are the absence of a lymphatic system within the brain and spinal cord, dense dura, and lack of a nurturing stroma. It is very rare to see direct extra-cranial infiltration and skull base extension of either

GBMs or gliosarcomasbut rarely functional lymphatic vessels in the dural sinuses connected to the deep cervical lymph nodes have also been seen. (11)Müller et al. found in a study from 2014 that more than 20% of patients with primary GBM had circulating tumor cells in the peripheral blood, confirming the potential of these cells to escape the intracerebral environment and survive for a not negligible amount of time in the bloodstream. (20)

Haematogenous metastases may result from invasion of the intratumoral vessels and trans-dural penetration into the dural sinuses caused by craniotomy procedures or cranial irradiation. Repeated surgical resection and ventricular shunting can cause dissemination of tumor cells into the blood stream.(13) The reason for extracranial metastasis in our patient may be due to dural location and VP shunt placement leading to extensive extra cranial metastasis. (13)

Due to the rarity of gliosarcomas, similar biological similarities, unclear mechanisms of pathogenesis, and limited clinical experience, clinical management of these tumors is challenging. They are usually treated as GBM, with modalities including tumor resection, postoperative radiation therapy, and chemotherapy with oral Temozolamide as per Stupps Trial. (21,22)

Different combinations of chemotherapy as nitrosureas, misonidazole, dacarbazine, mithramycin, ametophterin, thalidomide, temozolomide, irinotecan, vincristine, cisplatin, or doxorubicin have been tried. The total dose delivered in radiotherapy ranged from 45 to 81 Gy in these reports.(23,24,25)There may be differential sensitivities to radiation of the gliomatous and sarcomatous elements as was seen in a case report describing recurrence of only the sarcomatous component of a PGS after boron neutron capture therapy. (24)

Currently, there is very little data regarding the response of GSM to novel therapies that are being developed and studied for malignant gliomas, such as immunotherapy and cancer vaccine therapies. Most trials with malignant glioma include GSM as a variant of GBM, and roles of novel therapies in management of GSM becomes difficult to determine (25) Current evidence suggests that angiogenesis inhibitors may have clinical utility for GBM patients. Although bevacizumab has been recently approved for use as a single agent for patients with GBM, with progressive disease, most of the molecular targeted therapy phase II clinical trials in GBM have not translated into significant survival advantages. (26)

In future, attention needs to be focused on the cellular and molecular biology of gliosarcoma pertaining to tumor proliferation, invasion, angiogenesis, interaction with extracellular matrix and promoter methylation status of the DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT), and amplification of EGFR. Studies have shown a strong association between MGMT promotor-methylated tumors and PTEN positivity with improved survival. (25)

It has a median survival in untreated patients of 4 months and from 6.25 to 11.5 months in treated patients. (3,27). The mean overall survival of patients receiving radiotherapy is longer (10.6 months) than for those treated only with surgery (6.2 months). (28)The prognosis for GS is generally poor, with a mean survival of 10.5 months since time of GS diagnosis (range 4.5-21 months). (24) In our case the patient survived for 9 months after gliosarcoma diagnosis. The brain edema with increase in intracranial pressure and herniation of the temporal lobe are usually the immediate causes of death.

Several factors are associated with overall survival in GBM patients, including clinical and genetic parameters. Based on the available literature, clinical parameters, such as young age, predominance of female sex, aggressive surgical resection, and adjuvant RT in GBM, are generally associated with better prognosis. Similarly, these clinical factors affect GSM survival. Patients diagnosed with GSM prior to 50 years of age have a median survival of 15 months compared with 7 months for those diagnosed after age 50. Patients treated with gross total resection and adjuvant radiation have a significantly higher median survival rate. (7)

In addition, a number of molecular factors are associated with a favourable prognosis in GSM patients. These factors include MGMT promoter methylation, EGFR, and PTEN protein expression. (25), (29) MGMT promoter methylation in glioma is associated with tumor regression as well as prolonged overall and disease-free survival. (1), (29), (30)

The prognosticsignificance of IDH1 or IDH2 mutations to GSM remains unknown, which might be associated with the low mutation rate. EGFR amplification in glioma is associated with tumor invasiveness, angiogenesis, poor survival, and resistance to radiation therapy. EGFRamplification is common in glioblastoma, and the rate of EGFR amplification is much lower in GSM, barely accounting for0% to 8% of cases. (25)Our patient was MGMT Methylation positive but IDH mutation negative, EGFR status was not tested.

The GSM distinguishing features from GBM may be gross macroscopic features,genetic alterations and the greater propensity to metastasise extracranially.It has a slightly worse prognosis than GBM although some cases of long surviving patients have been described. Genetically they have a similar profile to primary glioblastoma, except for a much lower frequency of epidermal growth factor receptor amplification (8%) in small series versus up to 50% of primary GBMs).Imaging features of GSM may be identical to GBM except intratumoral strip enhancement in GSM and insufficient to distinguish both entities.

CONCLUSION

GS represents a clinically challenging group of tumors, due to its rarity, poor prognosis, and the limited experience in published literature .They are often supratentorial with temporal lobe predilection, peripheral, frequently abutting or involving dura or falx, well demarcated tumors with solid and cystic components and moderate to extensive surrounding edema, their potential to appear similar to a meningioma grossly at operation, their increased metastatic potential, and the infrequency of EGFR mutation. Contrast enhanced T1weighted images showed heterogeneity, frequently with uneven and thick walled rim like or ring like enhancement, as well as intratumoral strip enhancement. Intratumoral strip enhancement may help in raising suspicion of gliosarcoma on MRI images preoperatively.Evaluation for extra-cranial disease may be necessary in gliosarcomas at diagnosis, and surveillance is required because of the propensity for hematogenous spread. Whole body PET scan with contrast should be done to rule out metastasis spread in case of any suspicion. In future, attention needs to be focused on the cellular and molecular biology of gliosarcoma pertaining to tumor proliferation, invasion, angiogenesis, interaction with extracellular matrix and promoter methylation status of the DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT), and amplification of EGFR. These might bring hope to improve outcomes in patients diagnosed with gliosarcoma.

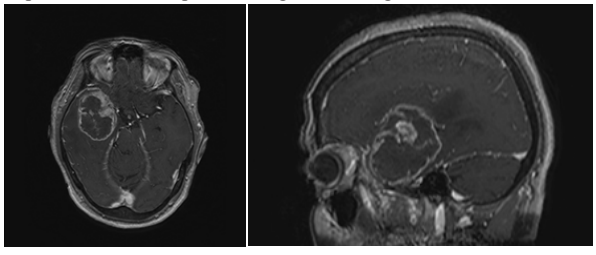

Fig. 1 MRI images of gliosarcoma.

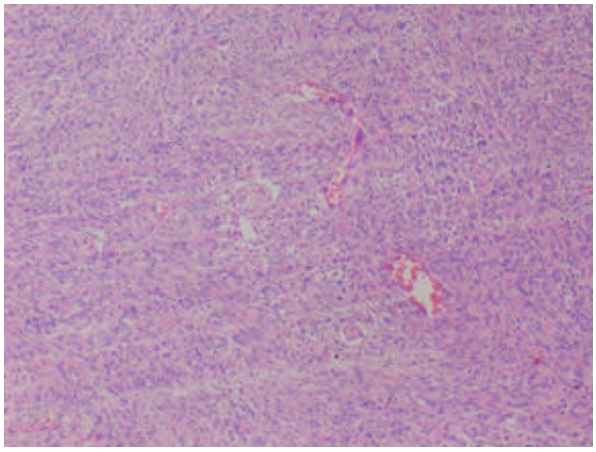

Fig. 2 Low power H&E stain showing admixture of glial and sarcomatous component.

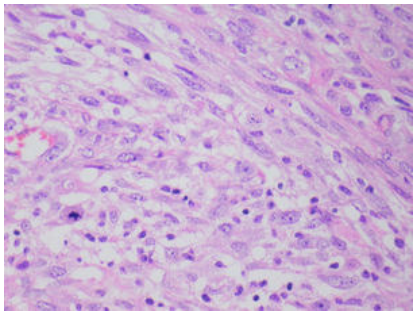

Fig 3- High power with prominent spindle cells with focal necrosis.

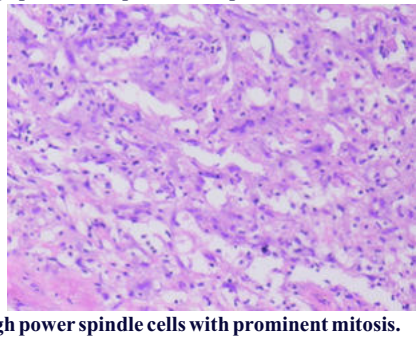

Fig 4- High power spindle cells with prominent mitosis.

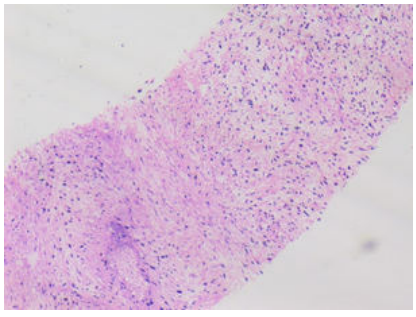

Fig 5- section from lung showing sarcoma deposits.

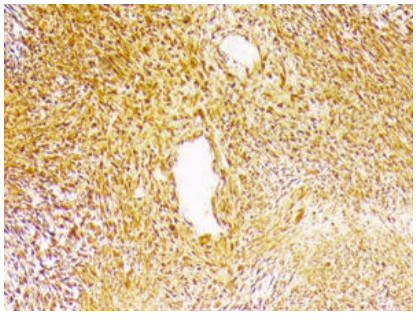

Fig 6- Vimentin staining highlighting spindle cells in brain.

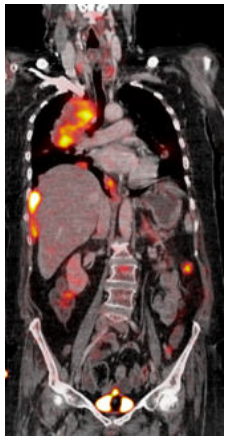

Fig 7- PET image showing multiple sites of metastasis – Pleural, lung, liver, adrenal, gall bladder, C3, L2 and thyroid metastasis.

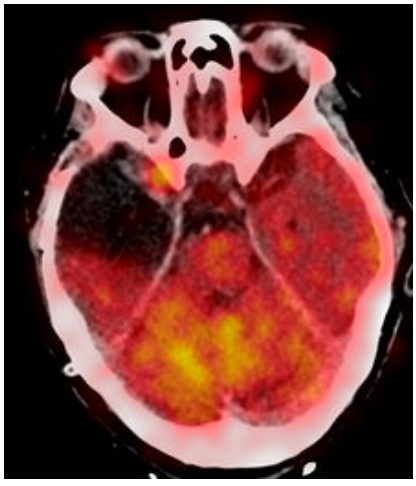

Fig 8- PET scan showing absence of FDG avidity in brain.

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