Pseudoprogression Following Concurrent Temozolomide and Radiotherapy in a Patient with Glioblastoma: Findings on Functional Imaging Techniques

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Pseudoprogression Following Concurrent Temozolomide and Radiotherapy in a Patient with Glioblastoma: Findings on Functional Imaging Techniques

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Abstract Concurrent temozolomide (TMZ) and radiotherapy became the new standard of care for patients diagnosed with glioblastoma multiforme (GBM). Recently, there has been an increasing awareness of progressive and enhancing lesions on MR images immediately after treatment. These lesions may be a treatment effect, so-called pseudoprogression. We experienced one case pathologically and clinically diagnosed as pseudoprogression. The lesion showed a high apparent diffusion coefficient on diffusion-weighted imaging, low blood volume on perfusion imaging, and low uptake of 18F-fluorodeoxyglucose on positron emission tomography. The lesion was pathologically diagnosed as pseudoprogression after additional surgical resection.

Key words: Glioblastoma; Chemoradiotherapy; Pseudoprogression; Magnetic resonance (MR) imaging; Positron emission tomography (PET)

Introduction

Treatment with concurrent temozolomide (TMZ) and radiotherapy is the new standard of care for patients with newly diagnosed glioblastoma multiforme (GBM)12). Since the introduction of chemoradiotherapy, there has been an increasing awareness of progressive and enhancing lesions on MR images, noted immediately after the end of treatment, which are not related to tumor progression but to the effects of treatment34). This so-called pseudoprogression can occur in up to 9~30% of patients who have been treated with TMZ chemoradiotherapy3~6). Conventional MR techniques, such as T2- and gadolinium-enhanced T1-weighted imaging, are limited in their ability to distinguish tumor recurrence from pseudoprogression. Clinically, the question of whether there is active tumor growth or pseudoprogression, has important consequences, and a reliable distinction between the two conditions is therefore crucial. Functional imaging methods, such as diffusion-weighted (DW) imaging and proton magnetic resonance spectroscopy (MRS), are expected to help distinguish between the two, but their value is not yet established7~11). Here we report a case pathologically and clinically diagnosed as pseudoprogression along with the radiological findings of DW imaging, perfusion-weighted (PW) imaging, and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Case report

A 54-year-old woman with aphasia was found to have a ring-enhancing brain mass on MR images (Figs. 1a~c). The mass was located in the left parietal lobe, was 50 mm long in diameter and was irregularly shaped. There was another
10-mm enhancing nodule medial to the main enhancing mass (Fig. 1c). DW imaging was performed at b values of 0 and 1000 s/mm² by applying the motion-probing gradients in the three orthogonal axes. Subsequently, isotropic DW images and maps of the isotropic apparent diffusion coefficient (ADC) were generated. The enhancing masses appeared bright on the isotropic DW images (Fig. 1d) and their ADCs were as low as that of the adjacent normal-appearing cerebral white matter (Fig. 1e). PW imaging was performed while a bolus of gadolinium–diethylenetriamine pentaacetic acid (0.1 mmol/Kg) was intravenously injected at a rate of 5 ml/s. Voxel-wise mapping of blood volume revealed that the tumor had a high blood volume, as high as that of the cerebral grey matter (Fig. 1f). The mass was suspected to be abundant in cells and vascularity, and was thought most likely to be GBM. A partial resection of the tumor was performed, and the pathological diagnosis of GBM was made (Fig. 2). The MIB-1 staining index was 12.6%.

Postoperative MR images obtained one day after the resection showed a small nodular residual enhancement medial to the surgical cavity (Fig. 3). TMZ and radiotherapy were performed concurrently after the operation. A radiation dose of 60 Gy/6 weeks and was given concurrently with TMZ (75 mg/m²) for 6 weeks.
There was no neurological deterioration during the treatment period. MR images obtained at the end of chemoradiotherapy revealed that the residual enhancing lesion increased in size, showing a ring-like enhancement (Figs. 4a–b). The mass showed iso- to hypo-signal intensity on isotropic DW images compared to the normal brain tissue (Fig. 4c), and its ADC was higher than that of the normal white matter (Fig. 4d). In maps of blood volume, the enhancing lesion showed a lower blood volume than the normal white matter (Fig. 4e). According to FDG-PET, the lesion showed a relatively low uptake maximum standardized uptake value (SUVmax) = 4.6, which was slightly higher than that of the normal white matter (Fig. 4f). Thus the enhancing lesion had a different appearance than the original tumor in maps of ADC and blood volume. However, since the possibility of the tumor progression could not be completely ruled out, additional tumor resection was performed.

During the operation, the lesion appeared to be cystic, and a serous fluid was aspirated. The resected specimen of the enhancing lesion mostly consisted of edematous, highly gliotic cerebral tissue with fibrotic blood vessels and focal, small areas of coagulation necrosis (Fig. 5a). Residual glioma cells were focally noted (Fig. 5b). The MIB-1 staining index in this area was 10.2% ; however, the main MIB-1 positive fraction included the reactive components such as inflammatory cells and endothelial cells, and the glioma cells showed very low proliferative activity (Fig. 5c). There was also granulation tissue with chronic inflammatory infiltrates but without glioma cells in the vicinity of the surgical defect from the previous operation (Fig. 5d). The pathological findings were interpreted as residual glioma tissue reacting to the radiation, and we clinically diagnosed this lesion as pseudoprogres-
TMZ was continued after the second resection. There has been no recurrence for 18 months since the initial operation.

**Discussion**

Since the preliminary report by Stupp et al.\(^1\) and the more recent report of the randomized European and Canadian trial\(^2\) were published, the algorithm for the initial treatment of GBM has been substantially altered. These studies demonstrated that the use of chemotherapy (TMZ) in the initial treatment had a benefit for patients with GBM. They showed an improvement in median survival (14.6 vs. 12 months) and 2-year survival (27% vs. 10%) among the patients who received TMZ compared with those who did not.

In several reports, patients with GBM have been described to have subacute treatment-related reactions with or without clinical deterioration, namely by showing edema and sometimes contrast enhancement on MR images, suggestive of tumor progression. The subacute radiation effects have been termed pseudoprogression because, despite the clinical or radiological suggestion of tumor progression, these patients recovered or stabilized. In some studies of

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Fig. 4 MR images obtained at the end of chemoradiotherapy. A T2-weighted image (a) and post-contrasted T1-weighted image (b) show marked enlargement of the residual nodule. The solid component of the lesion shows an iso- to hypointensity on the DW image (c), and the ADC in the lesion was higher than that of the normal white matter (d). A map of blood volume (e) shows that the blood volumes in the lesions are lower than that in the white matter. \(^{18}\)F-fluorodeoxyglucose positron emission tomography reveals slightly higher uptake of the solid component of the lesion than of the normal white matter (SUV\(_{\text{max}}\) = 4.6) (f).
patients with GBM, pseudoprogression occurred in 9-30% patients\textsuperscript{3-6}. The pseudoprogression occurred on the first MR imaging done within 2 or 3 months after treatment. This timing is earlier than the typical time period in which radionecrosis, a late radiation effect, has been described to occur after radiotherapy alone\textsuperscript{120}.

Radionecrosis is a severe local reaction to radiotherapy, with signs of a disrupted blood-brain barrier, edema, and a mass effect on MRI. Radionecrosis generally occurs 3-12 months after radiotherapy, but can occur up to years and even decades afterwards\textsuperscript{5}. Its histopathological features include massive coagulation necrosis, edema, and gliosis in addition to fibrous thickening, hyalinization, and fibrinoid necrosis of the blood vessel walls, and finally occlusion of the vessels. On the other hand, the mechanisms of pseudoprogression are not known, and the reasons for the apparent increased frequency of pseudoprogression among patients treated with concurrent TMZ and radiotherapy are also not well understood. However, it has been hypothesized that the concomitant use of radiotherapy with chemotherapy may result in radiosensitization not only of tumor tissue but also the surrounding normal brain tissue, causing local inflammation, edema, and abnormal vessel per-

\textbf{Fig. 5} Pathological examination of the specimen at the additional resection. H&E (a, b and d) and MIB-1 staining (c). Most of the specimen shows edematous, highly gliotic tissue with focal coagulation necrosis (lower right) and fibrotic blood vessels (a). Residual tumor cells are focally noted (b); however, their MIB-1 staining index is low (c). Granulation tissue with chronic inflammatory infiltrates is noted near the surgical defect of the previous operation (d). Bar = 200 µm (a), 50 µm (b and c), 30 µm (d).
meability. Combination therapy may increase endothelial cell death, TMZ–induced DNA damage, and radiation-induced DNA and membrane damage, which will increase hypoxia, vascular permeability, and tissue necrosis, with a subsequent increase in contrast enhancement and edema on MR images\(^5\)-\(^7\). In the present case, histopathological examination revealed that the lesion mostly consisted of edematous, highly gliotic cerebral tissue with fibrotic blood vessels and isolated, small coagulation necrosis. The cerebral tissue focally contained a small number of residual tumor cells with reduced proliferative activity. The findings suggest that the glioma and the surrounding cerebral tissue responded to the chemoradiotherapy, but in a way that was clearly different from late radiation necrosis or tumor recurrence. The findings might represent the histopathology of at least a subset of pseudoprogression.

Clinically, the question of whether there is active tumor growth or pseudoprogression has important consequences, and a reliable distinction between the two conditions is important. Conventional MR techniques, such as T2- and gadolinium–enhanced T1–weighted imaging, are limited in their ability to discriminate between tumor recurrence and pseudoprogression. Some authors reported functional imaging methods, such as DWI, MRS, PWI and FDG–PET may help distinguishing between tumor progression and radiation injury or radionecrosis\(^7\)-\(^11\). Some of these reports seem to include cases with pseudoprogression. However, those cases with were mixed–up with cases with radiation necrosis, and they were analyzed without distinction, even though the two conditions are histopathologically distinct. Moreover, very few reports have presented pathological correlates of pseudoprogression that underlie the functional imaging findings.

DWI may be useful in distinguishing between tumor recurrence and pseudoprogression after radiotherapy. Hein et al.\(^8\) compared ADC values measured within an enhancing lesion among 12 patients with tumor recurrence and 6 patients with radiation injury, which was not equal to pseudoprogression, and found that ADCs within enhancing lesions in patients with recurrent tumors were lower than those within enhancing lesions in those with radiation injury. Two patients in their non–recurrence group exhibited contrast enhancement immediately after radiotherapy, and they are presumed to be cases with pseudoprogression rather than radionecrosis. In our case, the ADC value of the enhancing lesion after chemoradiation therapy was higher than that of the primary tumor, reflecting the lack of dense tumor proliferation in the pathological specimen (Fig. 5).

There is no previous report regarding a possible role of PW imaging specifically in distinguishing between tumor progression and pseudoprogression. Barajas et al.\(^9\) suggested that dynamic susceptibility–weighted contrast–enhanced perfusion MRI might be used to differentiate recurrence from radiation necrosis. In our case, the blood volume of the primary lesion before the operation was as high as that of the normal gray matter, whereas that of the enhancing lesion resected in the second operation was lower than that of the normal white matter, suggesting that the lesion had low vascularity.

Finally, FDG–PET may also be useful in differentiating between recurrent tumor tissue and pseudoprogression\(^7\). However, a previous report showed the low sensitivity and specificity of FDG–PET in differentiating recurrent tumor from radionecrosis\(^10\). The accuracy of this imaging method is limited by the high glucose utilization of the normal brain. The lesion in our case showed low uptake of FDG, which is consistent with the histologically proven low tumor viability.

The findings in our case suggest that functional imaging techniques such as DW imaging, PW imaging and FDG–PET may play important roles in distinguishing pseudoprogression from early
It has been suggested that a combination of this purpose, but it was not performed in our case. It has been suggested that a combination of DW imaging and MRS can improve the differentiation of recurrent tumors from treatment-related necrosis\(^{11}\). This combination may also be applied to pseudoprogression.

We reported a case of a pathologically and clinically diagnosed pseudoprogression in which DW imaging, PW imaging, and FDG–PET were considered to be useful in differentiating pseudoprogression from tumor progression. Further studies are needed to establish the relative usefulness of these imaging modalities.

**References**


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膠芽腫の化学放射線治療後に pseudoprogression を生じた一例：機能画像での所見

緒言：膠芽腫に対する temozolomide (TMZ) を用いた化学放射線治療後に生じた pseudoprogression の機能画像所見を報告する。

症例：失語を主訴とする 54 歳の女性の左頭頂にMRIでリング状増強を示す腫瘍が指摘された。当院脳外科において部分切除され、病理学的に膠芽腫と診断された。TMZ を用いた術後化学放射線治療が行われたが、治療後の MRI で残存腫瘍の画像上の増大がみとめられた。このとき拡散強調画像では、腫瘍内のみかけ上の拡散係数 (apparent diffusion coefficient, ADC) は正常白質より高く、灌流画像では血液量が正常白質より低かった。また、positron-emission tomography (PET) では、正常白質よりわずかに高い程度の糖代謝をみとめた。追加切除が行われ、病理学的には腫瘍細胞の増生はなく、浮腫状の gliosis と壊死、および放射線治療により分裂能を失った glioma 細胞がみとめられた。これらの臨床経過、画像および病理所見から、pseudoprogression と診断された。

考察：拡散強調画像での高い ADC、灌流画像での低い血液量、および PET での比較的低い糖代謝は、腫瘍の活発な増殖の欠如を反映していると考えられた。これらの機能画像の、pseudoprogression と真の腫瘍増大との鑑別における有用性が示唆された。