Differential Diagnosis of Glioblastoma Pseudoprogression: Challenges, Advances, and Diagnostic Approaches

Abstract

Distinguishing between glioblastoma pseudoprogression and true tumor progression is a critical consideration in the clinical management of glioblastoma patients. This review provides a comprehensive overview of the key aspects of the differential diagnosis, including clinical presentation, imaging findings, positron emission tomography (PET), clinical course, histopathology, and more. It emphasizes the importance of advanced imaging techniques, such as perfusion MRI, MR spectroscopy, and diffusion-weighted imaging, in improving diagnostic accuracy. The review also discusses the challenges in developing reliable models for differentiation and the potential of extracellular vesicles (EVs) as biomarkers for glioblastoma diagnosis. Additionally, a case report underscores the complex nature of the pseudoprogression and recurrence differential diagnosis, highlighting the need for interdisciplinary collaboration and follow-up. While advances have been made, larger collaborative efforts and more reliable models are required to enhance diagnostic precision in glioblastoma pseudoprogression differentiation.

Introduction

Differential diagnosis of glioblastoma pseudoprogression involves distinguishing between pseudoprogression (a treatment-related phenomenon) and true tumor progression. This is a critical consideration in the clinical management of glioblastoma patients. Here are key aspects of the differential diagnosis:

Clinical Presentation:

Pseudoprogression: Typically occurs within the first three months after completion of radiotherapy and chemotherapy. True Progression: Can occur at any time and is often associated with worsening or new neurological symptoms. Imaging Findings:

Pseudoprogression: On MRI, pseudoprogression may show contrast enhancement and increased T2/FLAIR signal, similar to tumor progression. True Progression: Typically exhibits continued growth on successive MRIs, with or without enhancement. Positron Emission Tomography (PET):

Pseudoprogression: May show increased uptake of radiolabeled amino acids (e.g., 18F-DOPA) in the peri-tumoral region but not in the tumor core. True Progression: Often exhibits increased radioligand uptake throughout the tumor. Clinical Course:

Pseudoprogression: May stabilize or improve clinically with time or supportive treatment. True Progression: Tends to result in clinical deterioration over time. Histopathology:

Pseudoprogression: Biopsy may reveal treatment-related changes, such as radiation necrosis or inflammation. True Progression: Biopsy may show viable tumor cells. Serial Imaging:

Pseudoprogression: Lesions may stabilize or resolve on subsequent scans. True Progression: Lesions usually continue to grow. Treatment Response:

Pseudoprogression: Responsive to conservative management or medical treatment. True Progression: Often requires a change in the treatment approach, such as additional surgery, radiation, or chemotherapy. Advanced Imaging Techniques:

Perfusion Imaging: Advanced techniques like dynamic susceptibility contrast perfusion MRI can help in differentiating between the two by assessing blood flow. Magnetic Resonance Spectroscopy (MRS): MRS can provide metabolic information that aids in the diagnosis. Clinical and Radiological Correlation:

Integrating clinical observations with imaging findings is essential in making an accurate diagnosis. Follow-Up:

Pseudoprogression is more likely to stabilize or improve over time, while true progression typically results in continued deterioration. Regular follow-up is crucial. Biopsy:

When there is uncertainty in the diagnosis, a biopsy of the lesion may be considered to confirm the presence of tumor cells. Distinguishing between pseudoprogression and true tumor progression in glioblastoma is a complex process. The clinical team must carefully evaluate clinical symptoms, imaging findings, and the patient's response to treatment. Advanced imaging techniques and, in some cases, histopathological analysis may be necessary for a definitive diagnosis.

The suspicious lesion may represent post-treatment radiation effects (PTRE) such as pseudoprogression, radiation necrosis or Glioblastoma recurrence [1].

Although the field of immunotherapy in glioma is developing rapidly, glioblastoma is still prone to recurrence under strong immune intervention. The major challenges in the process of immunotherapy are evaluating the curative effect, accurately distinguishing between treatment-related reactions and tumor recurrence, and providing guidance for clinical decision-making. Since the conventional magnetic resonance imaging (MRI) is usually difficult to distinguish between pseudoprogression and the true tumor progression, many studies have used various advanced imaging techniques to evaluate treatment-related responses. Meanwhile, criteria for efficacy evaluation of immunotherapy are constantly updated and improved [2].

A study aimed to investigate whether perioperative markers could distinguish and predict PsP from TeP in de novo isocitrate dehydrogenase (IDH) wild-type Glioblastoma patients. Methods: New or progressive gadolinium-enhancing lesions that emerged within 12 weeks after CCRT were defined as early progression. Lesions that remained stable or spontaneously regressed were classified as PsP, otherwise persistently enlarged as TeP. Clinical, radiological, and molecular information were collected for further analysis. Patients in the early progression subgroup were divided into derivation and validation sets (7:3, according to operation date). Results: Among 234 consecutive cases enrolled in this retrospective study, the incidences of PsP, TeP, and neither patterns of progression (nP) were

26.1% (61/234), 37.6% (88/234), and 36.3% (85/234), respectively. In the early progression subgroup, univariate analysis demonstrated female (OR: 2.161, P = 0.026), gross total removal (GTR) of the tumor (OR: 6.571, P < 001), located in the frontal lobe (OR: 2.561, P = 0.008), non-subventricular zone (SVZ) infringement (OR: 10.937, P < 0.001), and methylated O-6-methylguanine-DNA methyltransferase (MGMT) promoter (mMGMTp) (OR: 9.737, P < 0.001) were correlated with PsP, while GTR, non-SVZ infringement, and mMGMTp were further validated in multivariate analysis. Integrating quantitative MGMTp methylation levels from pyrosequencing, GTR, and non-SVZ infringement showed the best discriminative ability in the random forest model for derivation and validation set (AUC: 0.937, 0.911, respectively). Furthermore, a nomogram could effectively evaluate the importance of those markers in developing PsP (C-index: 0.916) and had a well-fitted calibration curve. Conclusion: Integrating those clinical, radiological, and molecular features provided a novel and robust method to distinguish PsP from TeP, which was crucial for subsequent clinical decision making, clinical trial enrollment, and prognostic assessment. By in-depth interrogation of perioperative markers, clinicians could distinguish PsP from TeP independent from advanced imaging [3].

Conventional structural MRI is insufficient for distinguishing pseudoprogression from true progressive disease, and advanced imaging is needed to obtain higher levels of diagnostic certainty. Perfusion MRI is the most widely used imaging technique to diagnose pseudoprogression and has high reported diagnostic accuracy. Diagnostic performance of MR spectroscopy (MRS) appears to be somewhat higher, but MRS is less suitable for the routine and universal application in brain tumor follow-up. The combination of MRS and diffusion-weighted imaging and/or perfusion MRI seems to be particularly powerful, with diagnostic accuracy reaching up to or even greater than 90%. While diagnostic performance can be high with appropriate implementation and interpretation, even a combination of techniques, however, does not provide 100% accuracy. It should also be noted that most studies to date are small, heterogeneous, and retrospective in nature. Future improvements in diagnostic accuracy can be expected with harmonization of acquisition and postprocessing, quantitative MRI and computer-aided diagnostic technology, and meticulous evaluation with clinical and pathological data [4].

The key features pseudoprogression will demonstrate include:

Magnetic resonance perfusion imaging: reduced cerebral blood volume (viable tumor will usually have increased rCBV)

Proton magnetic resonance spectroscopic imaging

low choline

ratio Cho/NAA ratio ≤1.4

increased lactate peak

increased lipid peak

the trace may also be generally flat (hypometabolic)

Apparent diffusion coefficient

tumors that respond to treatment and result in pseudoprogression will have elevated ADC values due to cell death ADC mean values ≥1300 x 10-6 mm2/s 8

Moassefi et al. reported the development of a deep learning model that distinguishes PsP from TP in Glioblastoma patients treated per the Stupp protocol. Further refinement and external validation are required prior to widespread adoption in clinical practice [5)].

Incorporating all available MRI sequences into a sequence input for a CNN-LSTM model improved diagnostic performance for discriminating between pseudoprogression and true tumor progression [6)].

Glioblastoma progression

see Glioblastoma progression.

Glioblastoma recurrence

see Glioblastoma recurrence.

Reviews

Extracellular vesicles (EVs) are membrane-bound particles released by all cells. Previous research has found that these microscopic vesicles contribute to intercellular signaling and communication. EVs carry a variety of cargo, including nucleic acids, proteins, metabolites, and lipids. The composition of EVs varies based on cell of origin. Therefore, EVs can serve as an important biomarker in the diagnosis and treatment of various cancers. EVs derived from glioblastoma (GBM) cells carry biomarkers, which could serve as the basis for a potential diagnostic strategy known as liquid biopsy. Multiple EV isolation techniques exist, including ultrafiltration, size exclusion chromatography, flow field-flow fractionation, sequential filtration, differential ultracentrifugation, and density-gradient ultracentrifugation. Recent and ongoing work aims to identify cellular markers to distinguish GBM-derived EVs from those released by noncancerous cells. Strategies include proteomic analysis of GBM EVs, identification of GBM-specific metabolites, and use of Food and Drug Administration-approved 5-aminolevulinic acid-an oral agent that causes fluorescence of GBM cells-to recognize GBM EVs in a patient's blood. In addition, accurately and precisely monitoring changes in EV cargo concentrations could help differentiate between pseudoprogression and GBM recurrence, thus preventing unnecessary surgical interventions [7)]

In summary, the article effectively highlights the potential of EVs as biomarkers in cancer, with a specific focus on GBM. It provides valuable insights into isolation techniques and strategies for distinguishing GBM-derived EVs.

Case series

A retrospective single-institution study included patients with isocitrate dehydrogenase (IDH) wild-type glioblastoma and a newly developed or enlarging measurable contrast-enhancing mass within 12 weeks after concurrent chemoradiotherapy. CBV, capillary transit time heterogeneity (CTH), oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen (CMRO2) were obtained from DSC-PWI. Predictors were selected using univariable logistic regression, and performance was measured with adjusted diagnostic odds with tumour volume and area under the curve (AUC) of receiver operating characteristics analysis.

A total of 103 patients were included (mean age, 59.6 years; 59 women), with 67 cases of TP and 36 cases of pseudoprogression. Pseudoprogression exhibited higher CTH (4.0 vs. 3.4, p = .019) and higher OEF (12.7 vs. 10.7, p = .014) than TP, but a similar CBV (1.48 vs. 1.53, p = .13) and CMRO2 (7.7 vs. 7.3s, p = .598). Independent of tumour volume, both high CTH (adjusted odds ratio [OR] 1.52; 95% confidence interval [CI]: 1.11-2.09, p = .009) and high OEF (adjusted OR 1.17; 95% CI:1.03-1.33, p = .016) were predictors of pseudoprogression. The combination of CTH, OEF, and CBV yielded higher diagnostic performance (AUC 0.71) than CBV alone (AUC 0.65).

High intratumoural capillary transit heterogeneity and high oxygen extraction fraction derived from DSC-PWI have enhanced the diagnostic value of CBV in pseudoprogression of post-treatment IDH-wild type glioblastoma.

Clinical relevance statement: In the early post-treatment stage of glioblastoma, pseudoprogression exhibited both high oxygen extraction fraction and high capillary transit heterogeneity and these dynamic susceptibility contrast-perfusion weighted imaging derived parameters have added value in cerebral blood volume-based noninvasive differentiation of pseudoprogression from true progression [8)]

This study offers a valuable contribution to the understanding of glioblastoma progression and pseudoprogression differentiation. The utilization of advanced imaging techniques and the inclusion of multiple parameters show promise in improving diagnostic accuracy. However, further research is warranted to confirm these findings and translate them into clinical practice. The potential benefits of accurate differentiation between pseudoprogression and TP in glioblastoma underscore the significance of such investigations.

In a single-center analysis, 105 patients with GB who developed a suspected imaging PsPD in the first 7 months after standard CRT were identified retrospectively. Imaging data included standard MRI anatomical sequences, apparent diffusion coefficient (ADC), and normalized relative cerebral blood volume (nrCBV) maps. Median values (ADC, nrCBV) and RFs (all sequences) were calculated from DL-based tumor segmentations. Generalized linear models with LASSO feature-selection and DL models

were built integrating clinical data, MGMT methylation status, median ADC and nrCBV values and RFs.

A model based on clinical data and MGMT methylation status yielded an areas under the receiver operating characteristic curve (AUC) = 0.69 (95% CI 0.55-0.83) for detecting PsPD, and the addition of median ADC and nrCBV values resulted in a nonsignificant increase in performance (AUC = 0.71, 95% CI 0.57-0.85, P = .416). Combining clinical/MGMT information with RFs derived from ADC, nrCBV, and from all available sequences both resulted in significantly (both P < .005) lower model performances, with AUC = 0.52 (0.38-0.66) and AUC = 0.54 (0.40-0.68), respectively. DL imaging models resulted in AUCs ≤ 0.56.

Currently available imaging biomarkers could not reliably differentiate PsPD from true tumor progression in patients with glioblastoma; larger collaborative efforts are needed to build more reliable models [9].

The inclusion of various imaging biomarkers and advanced modeling techniques underscores the complexity of the problem. The findings suggest that larger collaborative studies and the development of more reliable models are necessary to improve the accuracy of this differentiation. Accurate discrimination is essential for optimizing the treatment approach for GB patients, and this remains an area of active research and clinical need.

Case reports

A 74-year-old-male, previously treated with fronto-parietal craniotomy due to primary glioblastoma multiforme (GBM), followed by concurrent radiation therapy (RT) and temozolomide (TMZ) chemotherapy. Magnetic resonance imaging (MRI) of the brain, at 1 month after completing RT + TMZ, depicted partial response. Three months later, the patient was submitted to a further brain MRI, that resulted doubtful for therapy induced changes (i.e., pseudoprogression). The patient, who had been previously treated with prostatectomy for prostate cancer (PC), underwent a positron emission tomography/computed tomography (PET/CT) scan with 18F-choline for PC biochemical recurrence. 18F-choline whole body PET/CT resulted negative for PC relapse, while segmental brain PET, co-registered with MRI, demonstrated increased tracer uptake corresponding to tumor boundaries. In order to solve differential diagnosis between pseudoprogression and GBM recurrence, brain PET/CT with 18F-L-dihydroxy-phenil-alanine (18F-DOPA) was subsequently performed: fused axial PET/MRI images showed increased 18F-DOPA incorporation in the peri-tumoral edema, but not in tumor boundaries, consistent with the suspicion of GBM pseudoprogression, as then confirmed by clinical and radiological follow-up [10].

This case highlights the intricate diagnostic challenges faced in differentiating between pseudoprogression and GBM recurrence. It underscores the value of combining multiple imaging modalities, such as PET/CT with 18F-choline and 18F-DOPA, in the diagnostic process. Furthermore, it emphasizes the significance of clinical follow-up and interdisciplinary collaboration to ensure the best possible patient care. However, a discussion of potential limitations would enhance the case review.

Conclusions

In conclusion, while significant progress has been made in differentiating glioblastoma PsP from TeP, larger collaborative efforts and the development of more reliable models are essential to enhance diagnostic precision in this critical clinical challenge. This review emphasizes the need for interdisciplinary collaboration and close follow-up in the management of glioblastoma patients.

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