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Case report of recurrent anaplastic oligodendroglioma with mixed astrocytic components and pathological discordance of tumor progression

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ABSTRACT

We present a case of a patient with the initial diagnosis of oligoastrocytoma WHO grade II. After multiple previous treatments and transformation to an anaplastic oligoastrocytoma WHO grade III, imaging after radiotherapy showed another tumor progression. Histopathological analysis after tumor resection confirmed parts of an astrocytic and an oligodendroglial tumor with extensive therapy-related changes. This constellation is not sufficiently covered by the current classification system and currently described as a diffuse glioma.

1. Introduction

With the renewal of the WHO classification and a stronger focus on molecular genetic markers, diagnoses have also changed in some cases [1]. However, there is a possible weakness in the current classification system. Mixed tumors with astrocytically and oligodendroglially differentiated components are not adequately covered by the currently used tumor classification system [1]. Meanwhile, the diagnosis of an oligoastrocytoma is strongly discouraged in the current WHO classification [1]. Histopathological assessment and the distinction between pseudoprogress and pseudoresponse in MRI is sometimes very difficult [2–4]. There are currently no reliable criteria in standard MRI to differentiate between tumor progression and radionecrosis [3].

In a patient with multiple previous treatments of a brain tumor initially characterized as an anaplastic oligoastrocytoma WHO grade III, imaging after radiotherapy showed a tumor progression. Histopathological analysis after tumor resection confirmed parts of an astrocytic and an oligodendroglial tumor with extensive therapy-related changes. This constellation is not sufficiently covered by the current classification system and currently described as a diffuse glioma.

2. Case report

In 2008, the 23-year old male patient initially noticed a seizure disorder. At that time, imaging showed a left frontal tumor, which was surgically removed. According to the World Health Organization Classification (WHO) of Tumors of the Central Nervous System in use at this time (classification of 2007), the tumor was classified as a diffuse oligoastrocytoma WHO grade II. No additional molecular analyses to characterize the tumor were performed, and no further treatment was initiated. Postoperatively, the patient suffered from significant hemiparesis and aphasia; both recovered partially.

In 2012, imaging showed a recurrence and the tumor was resected again. The recurrence of an oligo-astrocytoma WHO II was confirmed histologically (classification of 2007) and combined radio-chemotherapy was carried out according to the Stupp protocol as indicated by the recurrence-situation [5]. A follow-up inspection of the material took place in 2019. Here, the tumor was characterized as O6-methylguanine–DNA methyltransferase (MGMT) methylated, Isocitrate dehydrogenase (IDH) 1 R132 H mutated with 1p19q codeletion.

In 2018, the frequency of epileptic seizures increased. Once again, imaging showed a recurrence with a new contrast enhancement frontal left. A stereotactic biopsy was carried out, which now revealed an anaplastic oligo-astrocytoma WHO grade III (classification of 2016). Cell and nuclear polymorphism, increased cell density, increased mitotic rate and pathological mitoses were described and valued as a sign of anaplasia. For identification of molecular markers there was too little material. Until May 2019, radio-chemotherapy was carried out. However, PCV (Procarbazine, Lomustine, Vincristine) had to be discontinued due to hematological disturbances.

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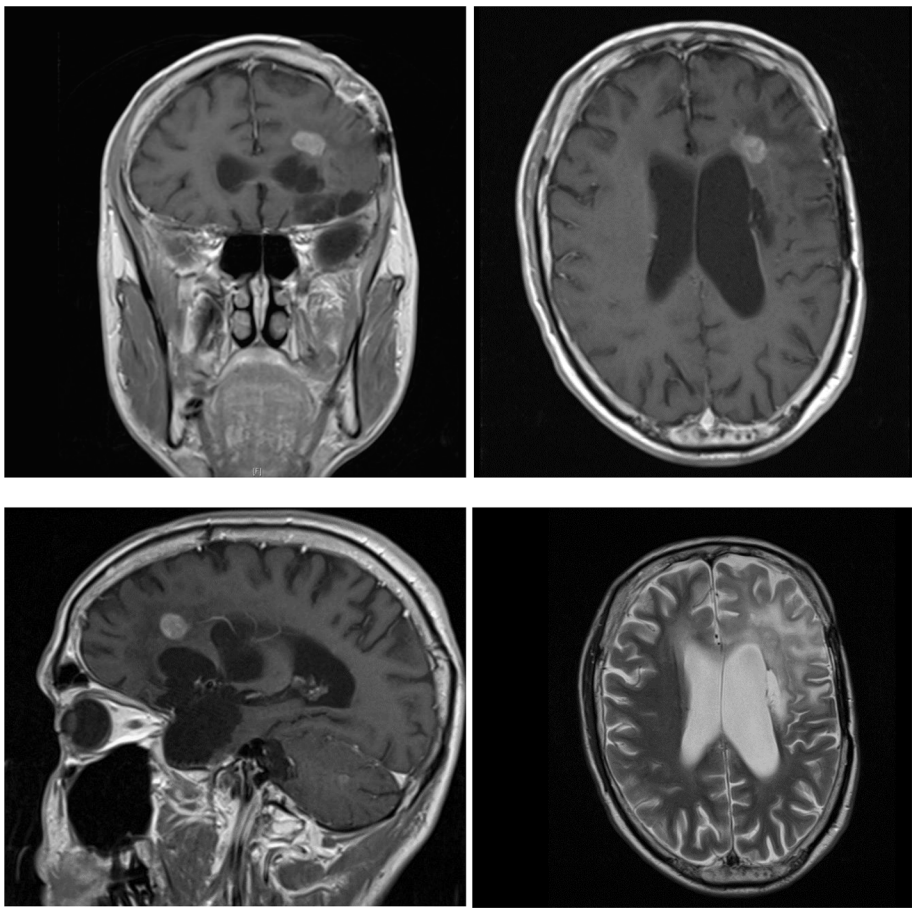

Fig. 1. December 2018: MRI (T1 with contrast coronar, axial, sagittal and T2 axial), Status before radiation.

Imaging in June 2019 showed a contrast enhancing, left frontal mass with possible central necrosis. At this time, radionecrosis was considered possible and follow-up was recommended In short-term follow-up MRI at the end of August 2019 the mass significantly grew in size (Figs. 1-3). At this point, the patient was admitted to our institution. Due to the continuing growth during the follow-up outside the main radiation field, imaging was assessed using the RANO (Response assessment in neuro-oncology) criteria and radiation-induced changes were ruled out by interdisciplinary tumor board decision, and another surgery was scheduled, which took place in September 2019. Intraoperatively, a firm tumor with central necrosis, comparatively clear boundaries to regular brain tissue, but strong 5-aminolevulinic acid-induced fluorescence was found. Histopathology revealed an oligoastrocytoma WHO II, MGMT methylated, 1p19q codeletion, IDH1 R132 H mutation, with extensive therapy-associated tissue alterations. The material was sent off for reference histology, which described a "diffuse glioma with predominant therapy-related changes" (classification of 2016); the tumor was characterized as IDH1 R132H mutated, Telomerase reverse transcriptase (TERT) mutated, MGMT methylated (Fig. 4). No adjuvant therapy was carried out. As yet, there is no evidence of a recurrence (Fig. 5).

3. Discussion

Preoperatively in 2019, we saw a contrast-enhancing mass outside the main radiation field, which significantly grew in size during short term follow up; this was associated with a clinical deterioration. According to the current standards, the criteria for a progressive disease were present [6,7]. Intraoperatively, the process showed strong 5-aminolevulinic acid-induced fluorescence. 5-aminolevulinic acid is currently used for intraoperative detection and improvement of the extent of resection in malignant gliomas [8,9].

In our case, there was no histopathological evidence of such malignancy despite distinct growth of the contrast enhancing mass and positive intraoperative immunofluorescence. These phenomena might have been caused by the previous treatments. There are case descriptions of malignant gliomas with suspected recurrence in which immunofluorescence could be detected intraoperatively, without detection of tumor tissue. These were assessed as "reactive changes" after previous radiation or chemotherapy [10,11]. It is also known that inflammatory changes and necrosis can be caused by radiation [4]. These can lead to pseudoprogression and radionecrosis. Risk factors for radionecrosis include young age and the combination with chemotherapy [3]. Hence, in our case, the patient was at high risk for radionecrosis.

There are currently no uniform criteria in standard MRI to differentiate between tumor progression and radionecrosis. Complementary imaging techniques such as perfusion, spectroscopy and diffusion may be used for this. However, interpretation of findings may be challenging: "These advanced techniques can be difficult to interpret given the heterogeneity of radionecrosis lesions and the frequent association of these lesions with evolving tumor tissues" [3]. In the literature we found indications that the use of perfusion imaging can be helpful in differentiating between pseudoprogression and tumor progression [12–14].

The distinction between pseudoprogression and radionecrosis is partially blurred. Some authors interpret radionecrosis as a form of pseudoprogression [2]. Pseudoprogression is more common in MGMT-positive tumors and is mostly asymptomatic [3]. The tumor was positive for MGMT-methylation in our case, but clinical deterioration was evident preoperatively. Pseudoprogression under therapy with Temozolomide has been reported frequently, whereas pseudoprogression under PCV has only been reported twice so far [15,16]. In the end,

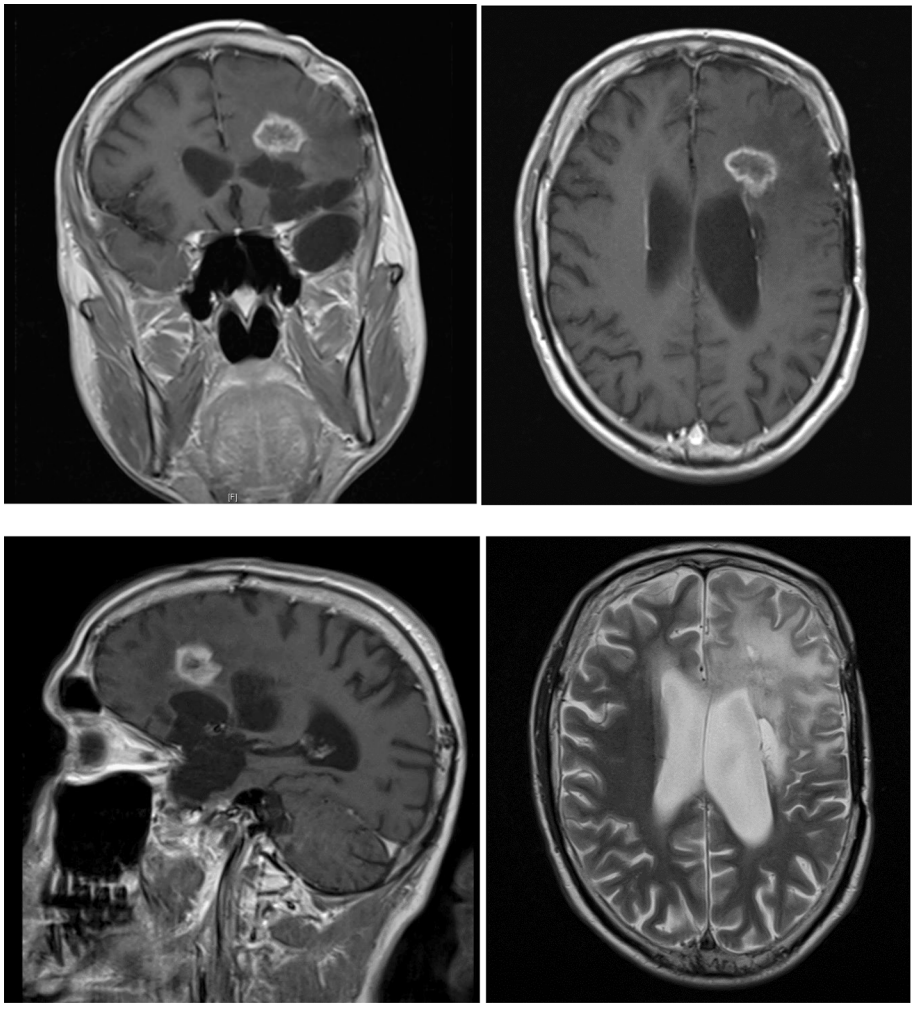

Fig. 2. May 2019: MRI (T1 with contrast coronar, axial, sagittal and T2 axial), suspected progress after radiation.

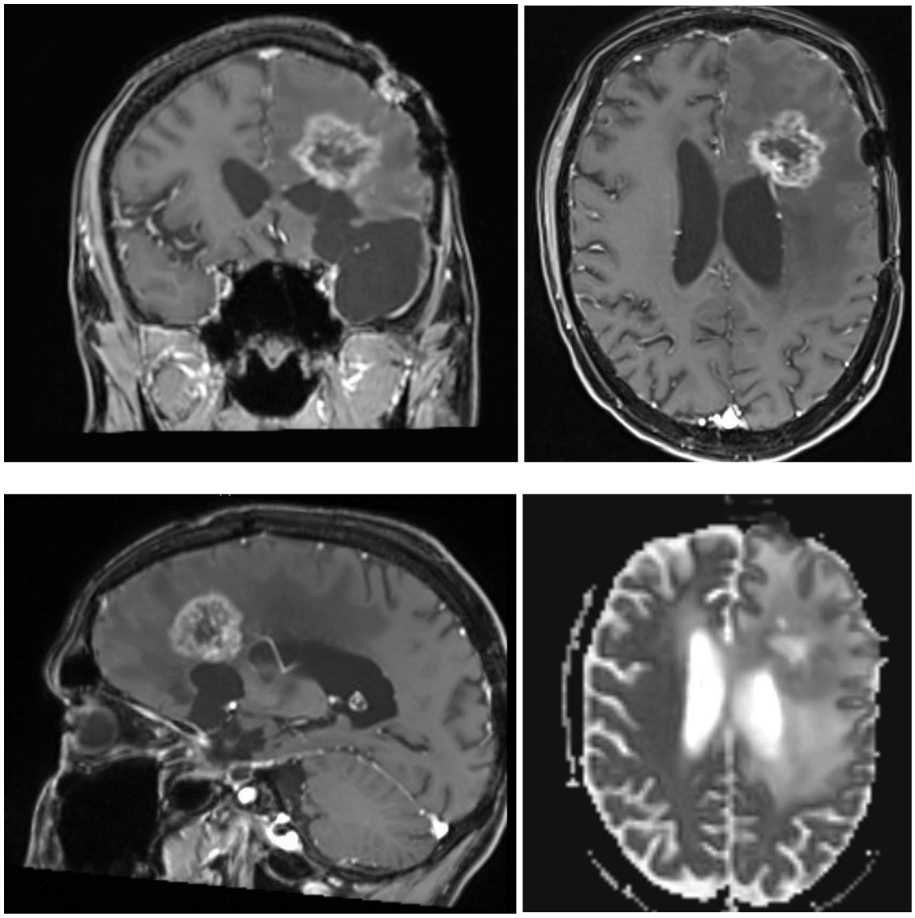

Fig. 3. August 2019: MRI (T1 with contrast corona, axial, sagittal and ADC axial), further progress, indication for surgery.

reference histology described a diffuse astrocytic glioma with an IDH mutation and pronounced therapy-related reactive changes. Detailed molecular biological assessment suggests that a mixed tumor with astrocytically and oligodendroglially differentiated components may be present, which is not adequately covered by the currently used tumor classification system [1]. Actually, the diagnosis of an oligoastrocytoma is strongly discouraged in the current WHO classification [1]. In our case, the 1p19q codeletion and TERT mutation were typical for an oligodendroglial tumor [17]. However, the astrocytic part of the tumor can be explained as composed of reactive astrocytes and so-called minigemistocytes which have been described in otherwise oligodendroglial tumors [18,19].

Some authors do not see oligoastrocytomas as a separate entity. In their opinion, oligoastrocytomas can be assigned to either oligodendrogliomas or astrocytomas by molecular genetic analysis. Changes in oligodendrogliomas with astrocytic features after radiation are therefore considered reactive [20]. Other authors consider oligoastrocytomas as an independent entity, which may contain areas with astrocytic differentiation as well as areas with oligodendrogial differentiation [21,22].

Summarizing all pre- and postoperative findings, we consider the progressively contrast-enhancing and space-consuming changes to be a tissue reaction to the radiation carried out in spring 2019. Retrospectively, the chemotherapy performed with PCV could also be related to this reaction. The decision to opt for another surgery, however, was made under the urgent suspicion of a life-threatening tumor progression. There was still no doubt about the progress after discussion in interdisciplinary tumor board and assessing the imaging using the RANO criteria, so no further imaging was required. In the future, further imaging (e.g. perfusion imaging) should be carried out in all patients for whom pseudoprogression is possible to be able to differentiate better between tumor progression and pseudoprogression and to avoid unnecessary surgery.

Our intraoperative impression – especially in terms of fluorescence behaviour - also seemed to confirm this presumption. However, surgery was most probably unnecessary in retrospect. The conflicting histopathological findings were interpreted as therapy-induced changes, but yet they may highlight a possible weakness in the current classification system. This case shows that a diagnosis that was initially “correct” could nevertheless change due to newer diagnostic methods or in general modifications of the classification, which could have a great impact on therapeutic decisions. The WHO classification has already been criticized several times regarding the classification of diffuse gliomas. An adaptation including new molecular genetic markers appears necessary [23,24].

4. Conclusion

With the renewal of the WHO classification and a stronger focus on molecular genetic markers, diagnoses have also changed in some cases. However, there is a possible weakness in the current classification system. Mixed tumors with astrocytically and oligodendroglially differentiated components are not adequately covered by the currently used tumor classification system.

The diagnosis of an oligoastrocytoma is strongly discouraged in the current WHO classification. In most cases, additional molecular genetic examination enables a clear assignment. As in the case shown here, this does not always work and remains controversal.

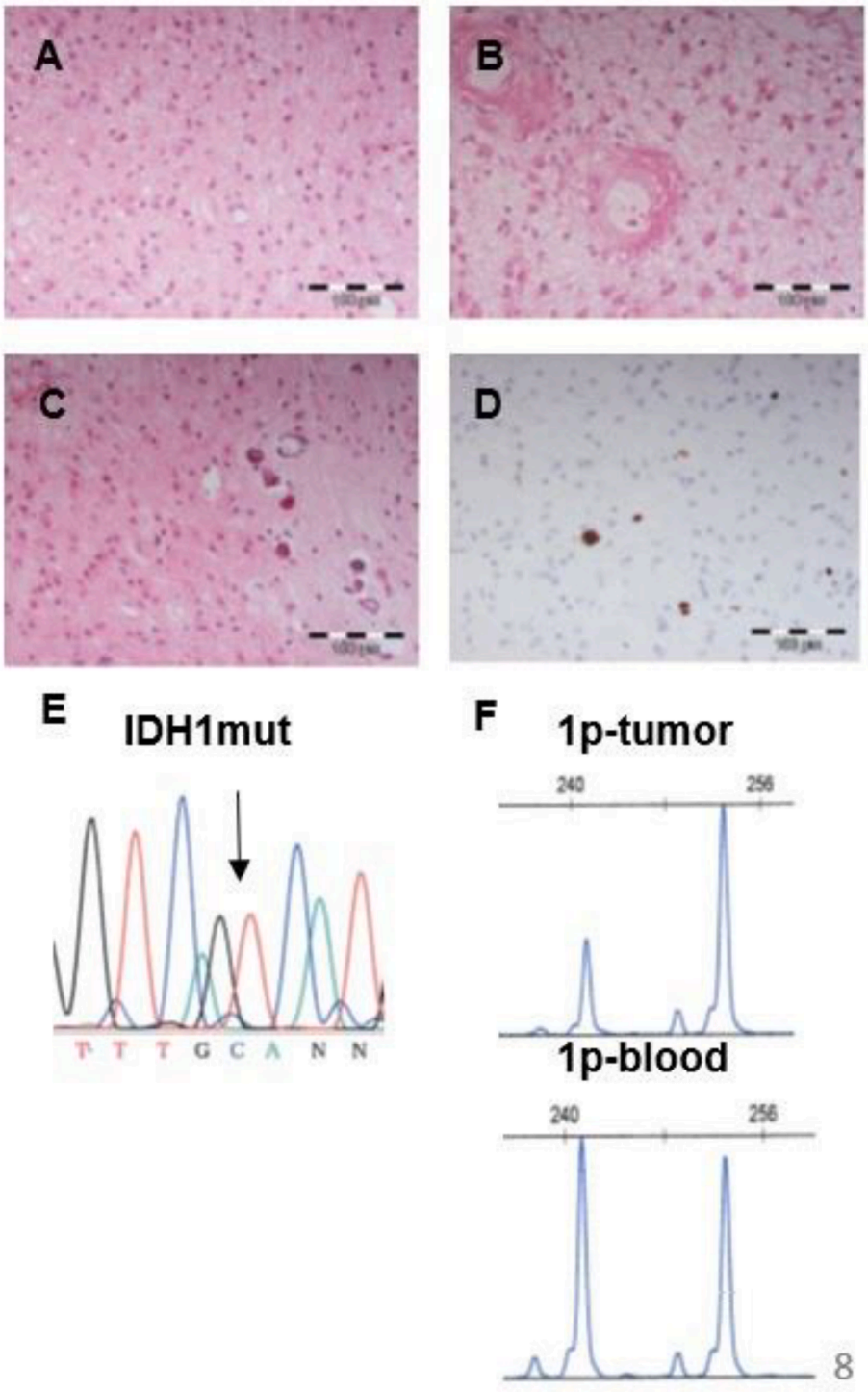

Fig. 4. Histopathological and molecular features of recurrent tumor. **A** Mixture of oligodendroglial and astrocytic (minigemistocytic) cells (H&E). **B** Hyalinized blood vessels and reactive astrocytes as dominating features in large parts of the tumor. **C** Focal calcifications. **D** Low proliferative activity seen in Ki-67 immunohistochemistry. **E-F** Molecular characterization of the 2019 tumor sample revealed an IDH1 mutation (R132H) (**E**) and a combined 1p/19q loss (shown for 1p in **F**) (upper panel: tumor, lower panel: blood).

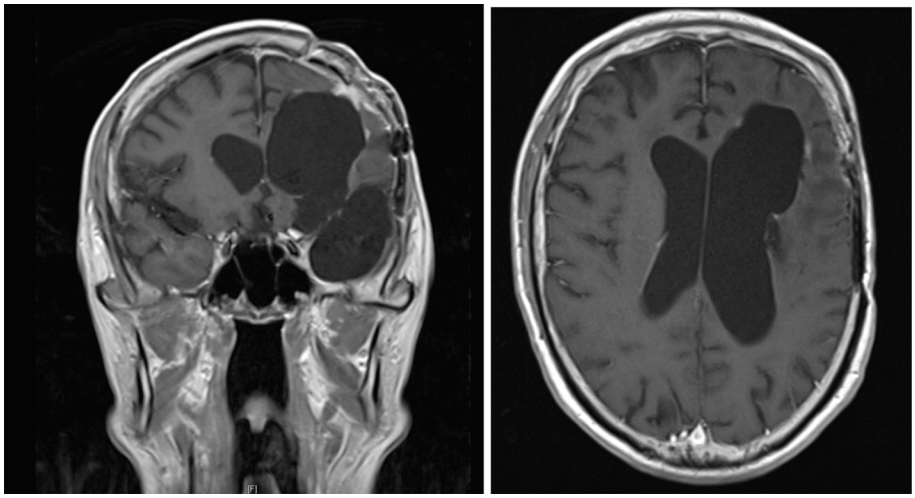

Fig. 5. March 2020: MRI (T1 with contrast coronar and axial), gross-total resection was achieved.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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