Differentiation between Recurrent Tumor and Radiation Necrosis in a Child with Anaplastic Ependymoma after Chemotherapy and Radiation Therapy

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Background: In patients after treatment for malignant brain tumors, a clear distinction between tumor recurrence and radiation necrosis can be challenging. This case report describes the diagnostic workup in a child with anaplastic ependymoma and inconclusive MRI (magnetic resonance imaging) and PET (positron emission tomography) findings.
Case Report: 1.5 years after resection, hyperfractionated radiotherapy and chemotherapy of an anaplastic ependymoma in the right parietal region, the cranial MRI of an 11-year-old girl showed multiple small contrast-enhanced lesions in the frontal cortex. In the following months, these lesions increased in number and size and neurologic symptoms developed. Diagnostic workup included repeated MRI scans, PET with an ^{18}F-amino acid and ^{18}F-fluorodeoxyglucose (FDG), as well as a brain biopsy.
Results: Amino acid PET, performed when the lesions were still small, showed multiple small areas of mild uptake in close correlation to the MRI lesions. Although not typical, this result was suspicious of tumor seeding, the more since the lesions appeared in gray matter areas outside the high-dose-rate irradiation field. A biopsy, performed 6 months later when the clinical appearance worsened, showed no tumor tissue. FDG PET, performed after the size and number of the lesions had increased, showed no intensely increased glucose metabolism, a high-grade recurrent tumor was therefore very unlikely. In the following months, the clinical picture stabilized.
Conclusion: The final interpretation of the lesions was multiple focal radiation necrosis based on perfusion abnormalities after chemotherapy and conformal hyperfractionated radiotherapy, probably due to an individually enhanced vulnerability of the cerebral vessels.

Key Words: Anaplastic ependymoma · Magnetic resonance imaging · Positron emission tomography · Hyperfractionated radiotherapy · Radiation necrosis

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Differenzierung zwischen Tumorrezidiv und Strahlennekrose bei einem Kind mit anaplastischem Ependymom nach Chemotherapie und Strahlentherapie

Hintergrund: Die Differenzierung zwischen Tumorrezidiv und Strahlennekrose bei Patienten nach Therapie von malignen Hirntumoren kann eine diagnostische Herausforderung darstellen. Dieser Fallbericht schildert den klinischen Verlauf und das diagnostische Vorgehen bei einer Patientin mit anaplastischem Ependymom und schwer zu interpretierenden magnetresonanz- (MRT) und positronenemissionstomographischen (PET) Befunden.
Fallbericht: 1,5 Jahre nach Resektion, hyperfraktionierter Strahlentherapie (Abbildung 1) und Chemotherapie eines anaplastischen Ependymoms im parietalen Kortex ergab das MRT eines 11-jährigen Mädchens multiple kleine Kontrastmittelanreicherungen im frontalen Kortex (Abbildung 2a). In den folgenden Monaten zeigte sich ein Zunahme der Befunde an Größe und Anzahl, klinisch entwickelte sich eine neurologische Symptomatik. Die diagnostische Palette beinhaltete neben wiederholten MRT PET mit einer ^{18}Fluor-markierten Aminosäure und ^{18}F-Fluordesoxyglucose. Ferner wurde eine Hirnbiopsie durchgeführt.
Ergebnisse: Das Aminosäure-PET zeigte kleine Areale mit schwacher Traceraufnahme in enger Korrelation zu den kleinen Läsionen im MRT (Abbildung 2a). Wenngleich nicht typisch, erschien dieser Befund als verdächtig für eine Tumoraussaat, da die Läsionen in einer Hirnregion auftraten, die außerhalb der Hochdosisregion des Bestrahlungsfeldes lag (Abbildung 1). Eine Hirnbiopsie, die 6 Monate später wegen zunehmender neurologischer Symptome erfolgte, erbrachte keinen Tumornachweis. Eine FDG-PET, durchgeführt bei Zunahme der Größe und Anzahl der Läsionen im MRT (Abbildung 2b), zeigte keinen intensiven Glucosestoff-

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wechsel in den Läsionen (Abbildung 2b) und ergab somit keinen Hinweis auf einen hochmalignen Hirntumor. In den folgenden Monaten stabilisierte sich das klinische Bild.

Schlussfolgerung: Abschließend wurden die Befunde als multiple fokale Strahlennekrosen auf der Grundlage einer vaskulären Störung nach Chemotherapie und Strahlentherapie, vermutlich einer individuell erhöhten Empfindlichkeit der zerebralen Blutgefäße, interpretiert.

Schlüsselwörter: Anaplastisches Ependymom · Magnetresonanztomographie · Positronenemissionstomographie · Hyperfraktionierte Strahlentherapie · Strahlennekrose

Introduction

Anaplastic ependymoma is a rare malignant brain tumor which constitutes 5–10% of primary brain tumors in the first 2 decades of life [9]. Therapy includes tumor resection, radiotherapy, and chemotherapy [20]. Despite improvement in therapy, the prognosis is often poor. Like in other malignant brain tumors, the differentiation between recurrent tumor and radiation necrosis with magnetic resonance imaging (MRI) can prove difficult. Positron emission tomography (PET) has evolved as a strong diagnostic tool for staging and therapy control in oncology [11–13, 16, 18]. This case report describes the clinical course and the diagnostic workup in a child with anaplastic ependymoma and inconclusive MRI and PET findings.

Case Report

In February, 1999, an 11-year-old girl was operated on for a brain tumor in the right parietal region. Histology revealed an anaplastic ependymoma T2 WHO grade III, and the girl was transferred to the University Hospital for complete tumor resection. After three-dimensional treatment planning, a conformal hyperfractionated radiotherapy with 2 × 1.2 Gy per day to the extended tumor region up to 66 Gy and a boost of 6 Gy to the immediate tumor region was applied with a linear accelerator (Figure 1). Irradiation was performed under mask fixation. Radiotherapy was followed by eight courses of chemotherapy with CCNU, vincristine and cisplatin. The entire treatment regimen was performed according to the HIT-MED '99 study protocol [19]. In September 2000, a tumor recurrence in the falx cerebri was suspected on an MRI, biopsy was performed, but histology revealed no tumor. At this time, on the MRI small foci of contrast-enhancing lesions appeared in white and gray matter structures of the right and left frontal cortex. To differentiate tumor spread from radiation necrosis, a PET with the ^{18}F-labeled amino acid ^{18}F-3-O-methy-fluoro-DOPA (^{18}F-3-OMFD) was performed in November 2000. The PET scan showed mild patchy tracer uptake in the frontal cortex; on the overlay of the PET data on the actual MRI (MPITOOL [15]), these mildly increased uptake sites were in close correlation to the MRI lesions (Figure 2a). Although the uptake of the amino acid was low, seeding seemed more likely than radiation necrosis, since most of the lesions occurred in an area outside the 40-Gy isodose of radiotherapy. From January 2001, the patient gradually developed a hemiparesis of the right side. A brain biopsy of the frontal cortex in May 2001 showed no tumor tissue and no fungal or bacterial infection. On MRI, the size and number of lesions increased, now showing an additional lesion of about 3 cm in diameter in the left parietal region involving white and gray matter structures. In June 2001, a PET scan with 18F-fluorodeoxyglucose (FDG) was performed. Since this scan revealed no increased glucose metabolism within the lesion, a high-grade recurrent tumor was very unlikely (Figure 2b). The differential diagnosis from MRI now included toxoplasmosis,

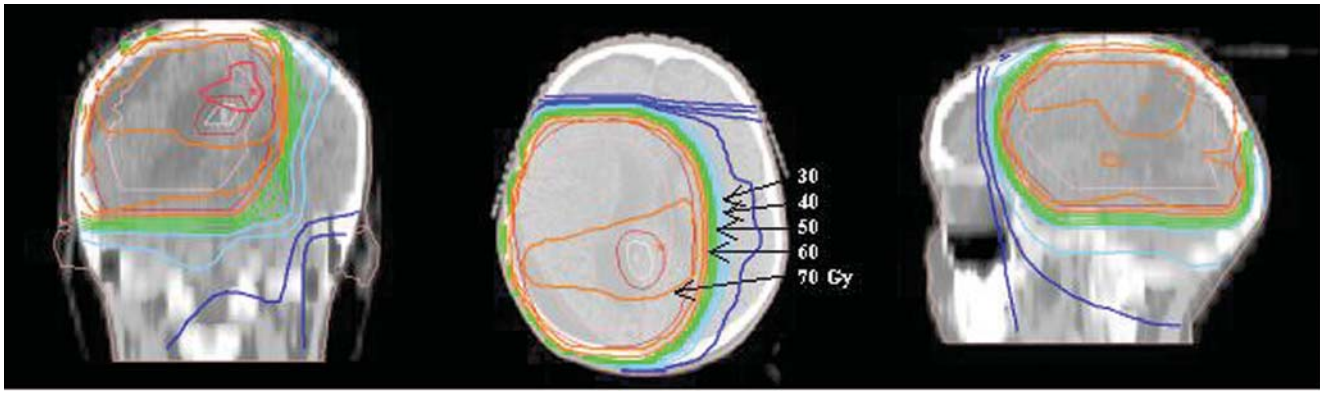

Figure 1. Summation of the radiation treatment plan in the coronal, transaxial and sagittal view.

Abbildung 1. Planaddition in koronarer, transaxialer und sagittaler Orientierung.

and therapy with trimethoprim and sulfamethoxazole was induced, showing no clinical benefit. In the following months, the clinical picture stabilized under intensive physiotherapy and corticosteroid medication. The MRI showed a decrease of brain volume and lesion size with impaired blood-brain barrier.

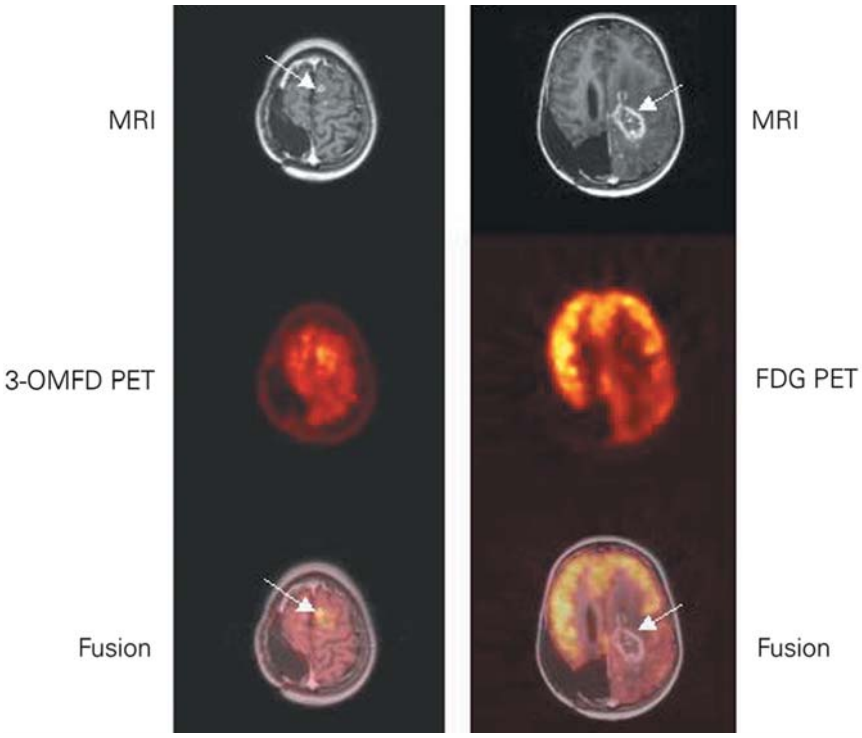

Figure 2a – Abbildung 2a **Figure 2b – Abbildung 2b**

Figures 2a and 2b. A) The 3-OMFD PET scan shows mild tracer uptake in close correlation to the MRI lesions (arrow). B) No intense glucose metabolism is found in the large subcortical lesion seen on MRI (arrow).

Abbildungen 2a und 2b. A) Die 3-OMFD-PET zeigt eine gering erhöhte Traceraufnahme in der im MRT abgrenzbaren Läsion (Pfeil). B) In der im MRT abgrenzbaren großen subkortikalen Läsion (Pfeil) zeigt sich kein stark erhöhter Glucosemetabolismus.

Discussion and Conclusion

MRI abnormalities after chemotherapy and radiotherapy for brain tumors can raise considerable interpretation problems. Tumor recurrence and radiation necrosis are the most common causes, their correct classification being mandatory for further therapy. PET can further characterize the lesions via functional information, i.e., glucose metabolism or amino acid transport. These informations complement the structural information from MRI [3].

The rationale for using radioactively labeled amino acids is the upregulation of amino acid transporters in brain tumors in contrast to normal brain tissue [10, 14, 21, 22]. Although a radioactive amino acid tracer for single-photon emission computed tomography (SPECT) exists as well, PET was applied to benefit from the scanner's high resolution of 4–5 mm in terms of the rather small lesions this patient showed at the time of investigation. 3-OMFD is a natural metabolite of L-DOPA, which behaves like an amino acid. Labeled with 18F [7], it shows high tumor-to-background ratios in brain tumors [2, 6, 8]. In this case, mild amino acid uptake was seen in close proximity to the MRI lesions. Although this was not a finding typical of tumor spread, the low uptake was thought to be in part attributed to partial volume effects. Furthermore, tumor seeding seemed more likely than radiation necrosis, since the lesions did not appear in the high-radiation field but in brain areas which received lower radiation doses which normally do not evoke radiation necrosis [1, 17]. In retrospect, the small areas with mild amino acid uptake most likely represented leakage of tracer from damaged vessels into brain tissue, a pathology occurring early in the development of necrosis, as described in the publication by Castel & Caillé [3].

The normal glucose metabolism of the brain shows high uptake in gray matter structures and low uptake in white matter areas. Brain tumors exhibit a wide range of glucose metabolism correlating with their grade of malignancy. High-grade tumors typically show a glucose uptake higher than normal gray matter, while in low-grade brain tumors the glucose metabolism is less than in normal gray matter [5]. Radiation necrosis normally shows very low glucose metabolism [4]. Since an anaplastic ependymoma is a highly malignant tumor and the lesion was mostly located in white matter, a high glucose uptake and a high contrast to the surrounding white matter structures could be expected in the case of recurrence. No intense glucose metabolism was found, a high-grade recurrent tumor was therefore very unlikely.

The final interpretation of the early and late brain lesions was focal perfusion abnormalities after chemotherapy and radiotherapy resulting in multiple areas of necrosis, most probably due to an individually enhanced vulnerability of the cerebral vessels.

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