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Adult anaplastic pilocytic astrocytoma – a diagnostic challenge? A case series and literature review☆

Michael Fiechter[a,1], Ekkehard Hewer[b,1], Urspeter Knecht[c], Roland Wiest[c], Jürgen Beck[a], Andreas Raabe[a], Markus F. Oertel[a,*]

[a] Department of Neurosurgery, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland
[b] Institute of Pathology, University of Bern, Bern, Switzerland
[c] Institute for Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland

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ABSTRACT

Introduction: Anaplastic pilocytic astrocytoma (APA) is an exceptionally rare type of high-grade glioma in adults. Establishing histopathological diagnosis is challenging and its clinical and radiological appearance insidious. By this case series and first literature review we investigated the various clinical, neuroradiological, and histopathological features of APA in adults.
Methods: An in hospital screening of the database from the Institute of Pathology was conducted to identify cases of APA. Further, we performed a literature review in PubMed using the keywords "anaplastic/malignant/atypical AND pilocytic astrocytoma" and "anaplastic astrocytoma/glioblastoma AND Rosenthal fibers" and summarized the current knowledge about APA in adults.
Results: Over the last decade we were able to identify 3 adult patients with APA in our hospital. According to the pertinent literature, the prognosis of APA in adults (documented survival of up to 10 years) appears to be better than in other high-grade gliomas. Few cases were associated with neurofibromatosis type 1, which seems to predispose for development of APA. Although molecular genetics is still of limited value for differentiation of APA from other high-grade glioma, advanced neuroimaging techniques such as magnetic resonance perfusion imaging and spectroscopy allow improved differential work-up. In particular, APA in adults has the ability to mimic various neurological diseases such as tumefactive demyelinating lesions, low-, or high-grade gliomas.
Conclusions: Although currently not explicitly recognized as a distinct clinico-pathologic entity it seems that adult APA behaves differently from conventional high-grade glioma and should be included in differential diagnostics to enable adequate patient care. However, further studies are needed to better understand this extremely rare disease.

1. Introduction

Pilocytic astrocytoma (WHO grade I) is generally perceived as a relatively homogenous entity characterized by young patient age at presentation, a limited number of predilection sites (e.g., cerebellum, brain stem, hypothalamus, and optic nerve), a low risk of recurrence or progression after gross total resection, and characteristic histopathological features (including Rosenthal fibers and a non-infiltrative growth pattern). However, very rarely tumors occur that resemble pilocytic astrocytoma, but show histological signs of anaplasia and follow an aggressive clinical course [1]. Such anaplastic pilocytic astrocytomas (APA) are particularly rare in patients older than 18 years of age [2].

Establishing a preoperative diagnosis of APA is challenging, as its clinical and radiological appearance is often unspecific. However, the clinical course of APA is perceived to be more favorable as compared to conventional anaplastic astrocytomas [3,4]. Here, we present 3 new cases with APA in adults diagnosed at our institution over the last decade and provide a first review of the current clinical, histopathological, and neuroradiological literature to update the reader's knowledge about APA.

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* Corresponding author at: Department of Neurosurgery, Inselspital, Bern University Hospital, Freiburgstrasse 10, 3010 Bern, Switzerland.
E-mail address: markus.oertel@insel.ch (M.F. Oertel).
[1] The first two authors contributed equally.

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2. Methods

A screening of our in hospital database from the institute of Pathology was performed to identify adult patients with APA. The need for ethical approval was waived by the institutional review board due to sole case reporting setting of the study.

By the use of 5 different combinations of keywords "anaplastic/malignant/atypical AND pilocytic astrocytoma" and "anaplastic astrocytoma/glioblastoma AND Rosenthal fibers" in PubMed we obtained 207 different articles. Thereafter; we selected those reports with documented cases of APA in adult patients by screening the abstracts. The references in the relevant articles were also taken into consideration. All pediatric articles and those cases containing malignant transformation of adult pilocytic astrocytoma into anaplastic variants due to prior radio-/or chemotherapy were excluded from further investigations. In those articles with limited information about the type of neoplasm, we tried to contact the corresponding authors to obtain further details. Only reports in English language were considered for our investigation.

3. Results

3.1. Case series

The in hospital database screening led to the identification of 3 adult patients with APA (cases 1, 2, and 3):

3.1.1. Case 1

A 52-year-old man with a history of pelviglossectomy and bilateral neck dissection for squamous cell carcinoma of the oral cavity 2 years previously was admitted with a 4-week history of gait disturbance and memory deficits. Neurological examination revealed no further deficits. Neuroimaging showed an irregularly enhancing mass lesion of the left precuneus (Fig. 1A,D). Presumed preoperative diagnosis was a high-grade glioma. Gross total removal of the tumor was successfully accomplished at our institution in 2008. The histopathological work-up showed a cellular astrocytic neoplasm with mitotic activity, microvascular proliferation, and infarct-like necrosis, which was remarkable for the presence of bipolar tumor cells in a myxoid background. Furthermore, occasional eosinophilic granular bodies and rare Rosenthal fibers were observed (Fig. 2D,E). Tumor cells were negative for R132H-mutant IDH1. Based on these findings, a diagnosis of APA was issued. After the operation the patient underwent fractionated stereotactic radiation therapy (6×5 Gy). 19 months later he presented with tumor recurrence with infiltration of the corpus callosum, which was considered non-resectable and without further alternative treatment options due to the patient's poor clinical state. Unfortunately, the patient died 3 months later, after a documented survival of 22 months.

3.1.2. Case 2

A 41-year-old male was referred with a 6-week history of double vision, left facial paresthesia, and weakness of the left limbs. Clinical examination showed left abducens and facial nerve paresis. Magnetic resonance imaging (MRI) demonstrated an irregularly enhancing tumor of the right pons, suggesting either inflammation or malignancy (Fig. 1B,E). Stereotactic biopsy was conducted in 2009. Histologically, astrocytic cells with plump bipolar processes and rare Rosenthal fibers characterized the tumor (Fig. 2F). However, there was an elevated Ki-67 proliferation index ranging between 5 and 10% and nuclear p53 accumulation, but there was no immunoreactivity for R132H-mutant IDH1. The tumor was classified as APA. For further treatment, the patient received fractionated radiation therapy (total dose of 54 Gy). The patient did not appear for regular follow-up appointments after completion of the 3-month long radiation therapy.

3.1.3. Case 3

A 60-year-old woman with known neurofibromatosis (NF) type 1 presented with visual disturbances, dizziness, and a change in mental state of 4-week duration. Further neurological status was normal. MRI showed a diffuse lesion in the thalamus, insula, and temporal white matter with indications of high-grade glioma, inflammation, or a metastatic lesion (Figs. 1C,F, 3 and 4). In 2009, a stereotactic biopsy was performed. The histological specimens revealed an astrocytic neoplasm characterized by the presence of Rosenthal fibers. While some of the fragments showed a low-grade component, others featured an elevated cellularity, consistent mitotic activity, glomeruloid microvascular proliferation, and nuclear p53 accumulation that qualified for classification as APA (Fig. 2A–C). Postoperatively, the patient was further treated by fractionated irradiation (30×2 Gy). Documented final follow-up was available 35 months after initial diagnosis.

3.2. Review of the literature

The literature review identified 20 articles (mostly single case reports) about anaplastic/malignant/atypical pilocytic astrocytoma or anaplastic astrocytoma/glioblastoma with Rosenthal fibers. By careful workup of these reports and exclusion of our 3 patients we obtained 31 cases of APA (Table 1). Notably, the cases described in Rodriguez et al., 2010 and 2011 (10 definitive APA cases) contained an unspecified number of subjects younger than 18 years of age (range 5–75 years) [1,5]. Historically, one of the first descriptions of APA in adults lasted back in the early nineties [6,7].

By systematic anatomical arrangement of the identified cases in Table 1, APA in adults seems to preferentially locate in the posterior cranial fossa. This is in contradiction to the common location of other types of high-grade glioma which mostly originate from the cerebral hemispheres.

In a study by Burkhard et al. 2 adult patients with APA provided documented long-term follow-ups of 7 and 10 years, respectively [4]. Similarly, we observed prolonged postoperative survival of up to 35 months in 1 of our patients (case 3). Compared to conventional anaplastic glioma the overall survival of adult patients diagnosed with APA appears to be improved.

New and advanced neuroimaging techniques such as MRI perfusion and spectroscopy allow improved differentiation between tumefactive demyelinating lesions, low-, and high-grade glioma which all can be mimicked by APA [8]. Typical imaging features of APA in adults are given in Figs. 3 and 4 (of case 3).

Finally, several cases of APA as well as 1 of our cases (case 3) were associated with NF type 1 which could predispose for this rare tumor entity [5,9].

4. Discussion

We report 3 new and remarkable cases of APA in adults with thorough diagnostic workup demonstrating the clinical, histopathological, and neuroradiological features relevant in diagnosis of this rare type of neoplasm. Moreover, our study presents one of the largest collections of APA in adult patients to date apart from an investigation that included various juvenile and adult cases of malignant transformation of pilocytic astrocytomas, NF-1 associated APA, and several histopathological occult cases [5,9]. In the literature, APA is frequently classified synonymously as anaplastic astrocytoma with abundant Rosenthal fibers, which includes uncommon and rare histologic features and was reported to occur in 5% of all patients diagnosed with pilocytic astrocytomas over a