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CASE REPORT

Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas—possible role of *Cannabis* inhalation

Mansoor Foroughi · Glenda Hendson · Michael A. Sargent · Paul Steinbok

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Abstract
Introduction Spontaneous regression of pilocytic astrocytoma after incomplete resection is well recognized, especially for cerebellar and optic pathway tumors, and tumors associated with Neurofibromatosis type-1 (NF1). The purpose of this report is to document spontaneous regression of pilocytic astrocytomas of the septum pellucidum and to discuss the possible role of cannabis in promoting regression.
Case report We report two children with septum pellucidum/forniceal pilocytic astrocytoma (PA) tumors in the absence of NF-1, who underwent craniotomy and subtotal excision, leaving behind a small residual in each case. During Magnetic Resonance Imaging (MRI) surveillance in the first three years, one case was dormant and the other showed slight increase in size, followed by clear regression of both residual tumors over the following 3-year period. Neither patient received any conventional adjuvant treatment. The tumors regressed over the same period of time that cannabis was consumed via inhalation, raising the possibility that the cannabis played a role in the tumor regression.
Conclusion We advise caution against instituting adjuvant therapy or further aggressive surgery for small residual PAs, especially in eloquent locations, even if there appears to be slight progression, since regression may occur later. Further research may be appropriate to elucidate the increasingly recognized effect of cannabis/cannabinoids on gliomas.

Keywords Pilocytic astrocytoma · Septum pellucidum · Fornix · Tumor regression · Cannabinoids · Cannabis

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Introduction

Spontaneous regression of a tumor may be defined as a clear decrease in the mass of a tumor without any medical intervention. For brain tumors, this has been previously described in non-NF1-associated pilocytic astrocytomas of the cerebellum, [23, 37, 44, 48, 49], thalamus [6], and temporal lobe [39], but not in the rare fornix/septum pellucidum location. Although referred to as spontaneous, the cause of regression may involve a combination of factors in any individual case.

We report two cases of spontaneous regression of PA in the fornix/septum pellucidum location, and discuss the possible influence of smoking *Cannabis* in these cases.

Patient presentation

Case 1

An 11-year-old girl presented with a 4-month history of intermittent headaches, which progressed to persistent headaches over 7 days, accompanied by a 2-day history of nausea, vomiting, and confusion. On examination, she had some blurring of the disc margins on fundoscopy and no focal neurological deficit. Computer tomography (CT)

and MRI scans demonstrated dilated lateral ventricles, and a mass lesion with ring enhancement in the region of the septum pellucidum. This appeared to be causing intraventricular obstructive hydrocephalus due to obstruction at the foramen of Monro (Fig. 1a, b).

She underwent surgery via craniotomy and interhemispheric transcallosal approach for resection of the tumor. A subtotal resection was carried out, leaving a small remnant at the most inferior aspect of the tumor in the region of the fornix. The procedure and recovery were uneventful. The histology was pilocytic astrocytoma (WHO grade 1) with a proliferative index of 2% (Fig. 2). Post-operative MRI scan 3 days later confirmed residual tumor; repeat MRI scans at

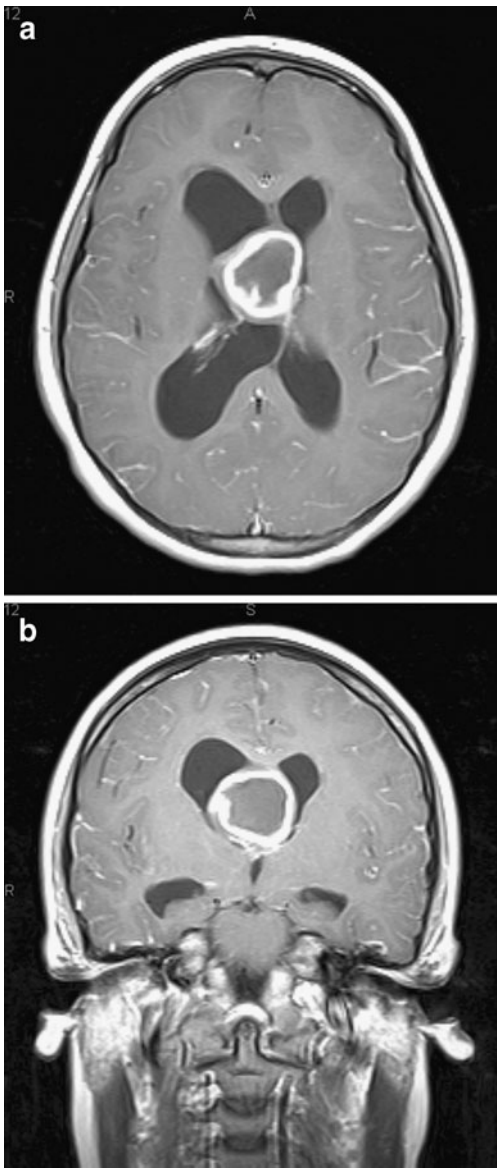

Fig. 1 **a** & **b** Case 1: Contrast-enhanced T1-weighted MRI scans in axial (**a**) and coronal (**b**) planes showing a large mass with peripheral enhancement in the septum pellucidum/forniceal region causing intraventricular obstructive hydrocephalus

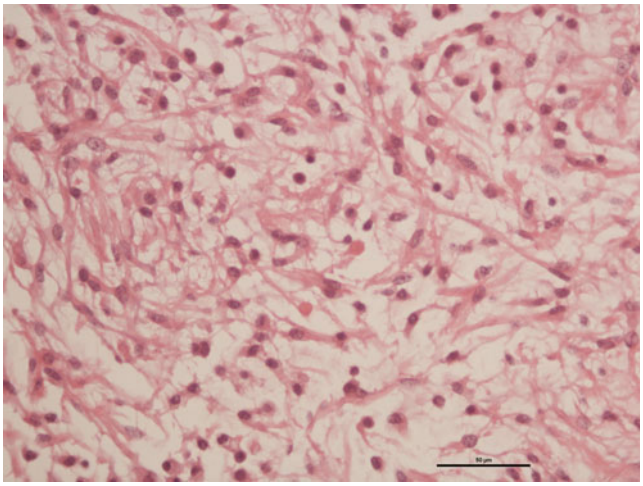

Fig. 2 Histologically, the tumor demonstrated the features of pilocytic astrocytoma with bipolar cells with "hair-like" cell processes, and eosinophilic granular bodies (H&E, ×400 magnification)

9 and 33 months post-operative demonstrated no change (Fig. 3a, b). However, over the following 3 years, there were clear radiological features of regression, and the lesion had almost disappeared 6 years post-surgery when she was aged 17 (Fig. 4a, b). The volume of tumor remnant was calculated using VOXAR volumetric software (VOXAR 3D version 6.3), and found to be 1.28 cm^3 at 9 months and 0.27 cm^3 at 6 years post-surgery. The only sequelae were mild psychological problems involving mood changes, and problems with short-term memory, which were also present prior to surgery. She had not received any other medical treatment, and there were no features suggestive of NF-1. The only significant feature in the history was the consumption of *Cannabis* via inhalation, on average three times a week. This occurred in the last 3 years of follow-up, namely between the ages of 14 and 17, and coincided with the time course of the regression of the residual tumor.

Case 2

A 13-year-old girl presented with a 5-day history of increasing headaches, nausea and vomiting. She also had a more prolonged history of short-term memory problems prior to her rapid deterioration. Following assessment and an emergency MRI scan, she was found to have intraventricular obstructive hydrocephalus due to a mass in the septum pellucidum near the foramen of Monro (Fig. 5a, b). She underwent emergency endoscopic biopsy, septostomy, and insertion of an external ventricular drain for cerebrospinal fluid (CSF) diversion. Following an inconclusive biopsy, she underwent a craniotomy and excision of the mass lesion. The tumor was seen to be in the septum pellucidum, displacing the fornices and foramen of Monro inferiorly. The approach was a transcortical transventricular route, utilizing the previous small cortical tract as the

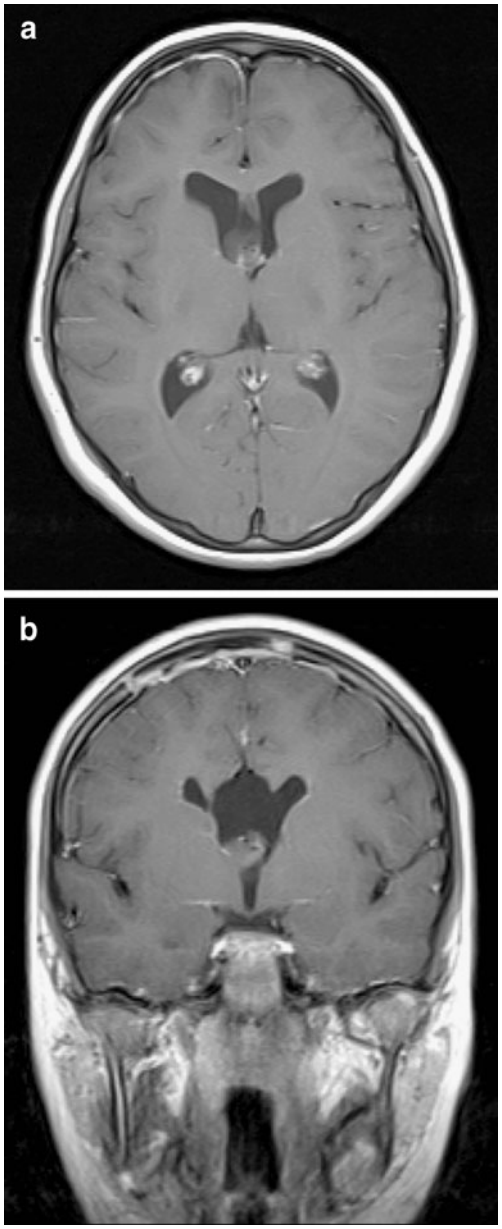

Fig. 3 **a** & **b** Contrast-enhanced T1-weighted MRI scans in axial (**a**) and coronal (**b**) planes 33 months post-resection show residual tumor at the foramen of Monro

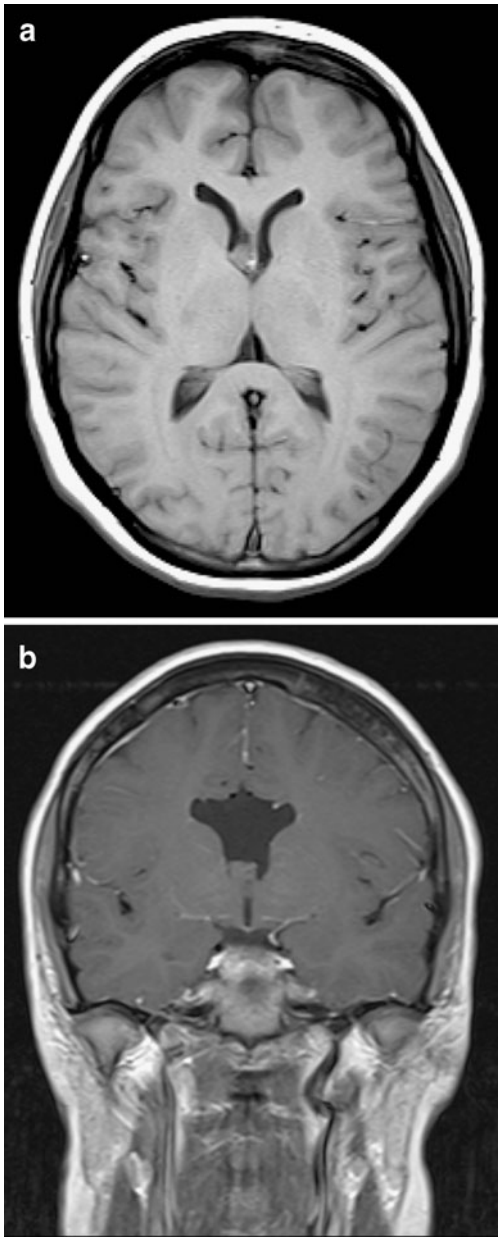

Fig. 4 **a** & **b** Contrast-enhanced MRI scans in axial (**a**) and coronal (**b**) planes 6 years post-surgical resection show regression of the tumor remnant, which was measured to be about 25% of early post-operative size

trajectory to the lesion. During the operation, it was thought that there was a subtotal resection of the lesion. She made an uneventful recovery and following discharge, gradually returned to normal schooling and was later able to go to higher education at university level without difficulties. Histologically, the tumor was confirmed to be a pilocytic astrocytoma (WHO grade 1) (Fig. 6) with proliferative index of 1%.

Follow-up scan 3 months later confirmed a small residual, and regular surveillance scans were carried out. There was slight growth of the remnant between the first post-operative scan at 3 months and the next scan done at 18 months post-operative (Fig. 7a, b). We elected to continue with observation, since she was clinically well. A scan done at 3 years post-operatively at 16 years of age showed slight decrease in the tumor volume (Fig. 8a, b), with further regression on later scans. The most recent MRI scan done 6 years post-operatively, when she was 19 years old showed almost complete disappearance of the tumor (Fig. 9a, b). The volume of tumor remnant was calculated to be 3.3 cm^3 at 18 months and 0.28 cm^3 at 6 years post-operatively. She did not receive any other medical treatment after the surgery, and there was no history of NF-1. The patient volunteered

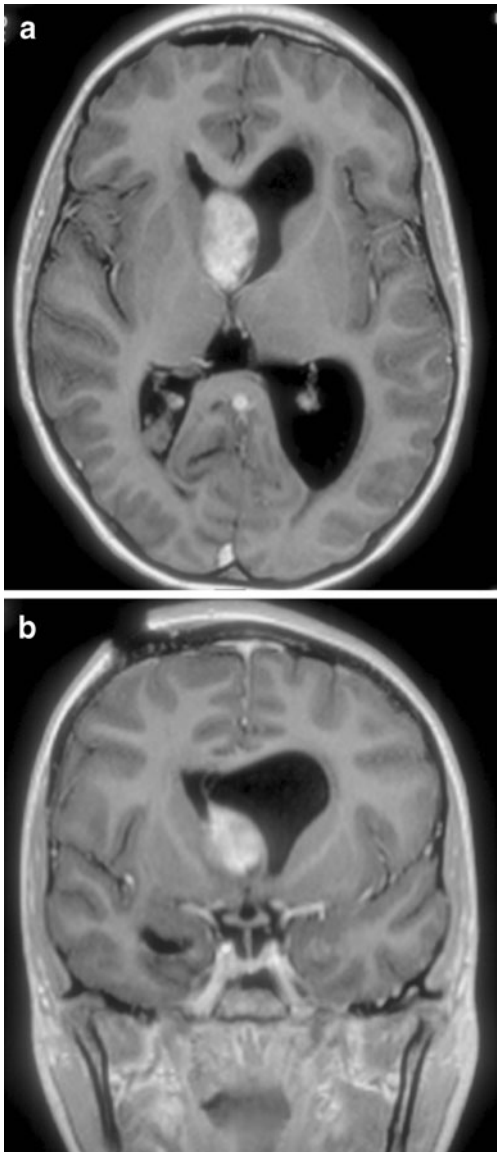

Fig. 5 **a** & **b** Case 2: Contrast-enhanced MRI scans in axial (**a**) and coronal (**b**) planes show the enhancing lesion in the septum pellucidum/forniceal region causing obstructive hydrocephalus. The right-sided burr hole made for endoscopic biopsy and temporary CSF diversion can be seen, as well as the remaining unilateral left-sided ventriculomegaly

information that she had smoked *Cannabis* occasionally starting at age 14, and on an almost daily basis from the age of 16 until her last follow-up when she was 19 years old. The regular use of *Cannabis* coincided with the time course of radiological tumor regression.

Discussion

Intraventricular tumors account for 5–10% of all intracranial pediatric tumors [50]. About 25% of these occur in the foramen of Monro region, some of which specifically involve the septum pellucidum. The only published

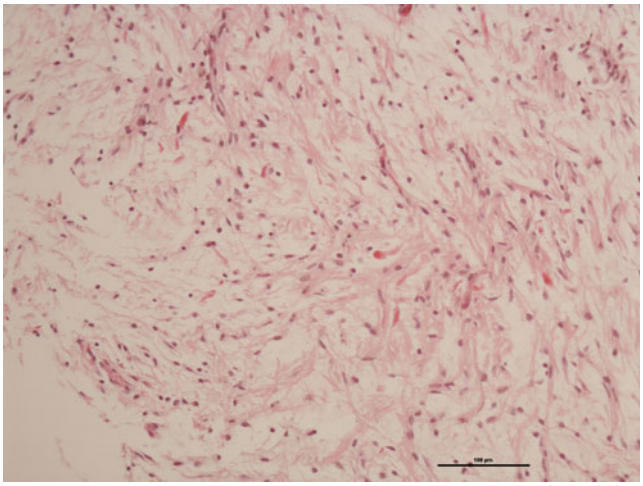

Fig. 6 Histologically, the tumor showed a pilocytic astrocytoma with low cellularity, bipolar cells, and Rosenthal fibers (H&E, ×200 magnification)

pediatric series of such septal tumors is by Blauwblomme et al. [7] consisting of eight cases, all low-grade gliomas in the forniceal region, half being pilocytic astrocytomas. All tumors were treated initially with surgical resection, but complete excision was achieved in only one patient. Two patients showed no progression of residual tumor without treatment on MRI surveillance; the remaining five cases received combinations of further surgery, chemotherapy, and radiotherapy. In our cases, the aims of surgery were to obtain tissue diagnosis, treat the hydrocephalus by restoring CSF flow (via excision and septostomy), and to achieve maximum cyto-reduction without causing new morbidity.

Progression of residual PAs is common and often anticipated during surveillance [2, 20], but it has become increasingly recognized that regression of PA residuals is not rare. There is no doubt that in both of our cases, there was residual tumor, which regressed without medical treatment. In both cases, the residual tumor was not simply an area of thin, linear enhancement, as may be seen in surgically induced post-operative change [9, 23]. The residual tumors were masses with measurable volume of persistent nodular enhancement, corresponding to the site where remnant was recorded to have been left behind. In one patient, the nodular enhancing mass increased initially on surveillance MRI before regressing later on.

This regression phenomenon has been well described in the cerebellum [17, 20, 23, 44, 46, 49]. Saunders et al. described 84 tumors in the posterior fossa treated surgically, including 14 cases with residual disease. Eleven did not receive adjuvant therapy, and 5 of the 11 tumors (45%) regressed during surveillance periods ranging from 7 to 66 months (mean of 32 months) [44]. Smootes et al. described spontaneous tumor regression in 4 (24%) of 17 patients with residual disease (tumor volume ranging from

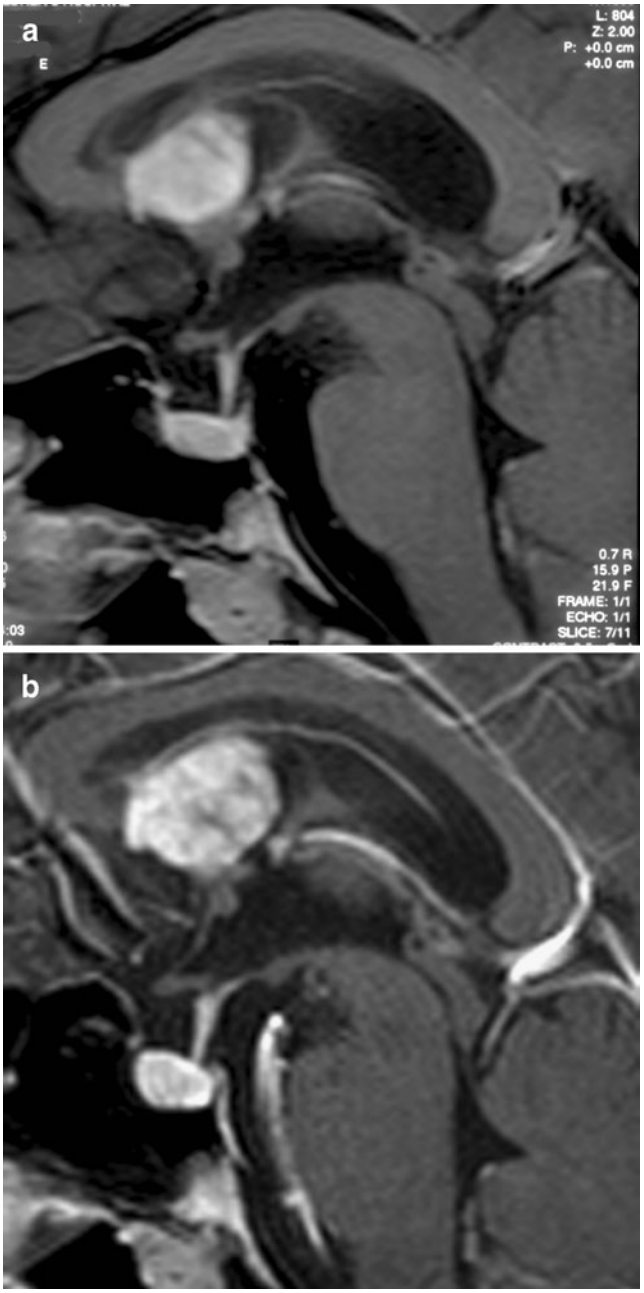

Fig. 7 **a** MRI at 3 months postoperatively. **b** MRI at 18 months post-op shows growth of the tumor remnant compared to the scan at 3 months post-op

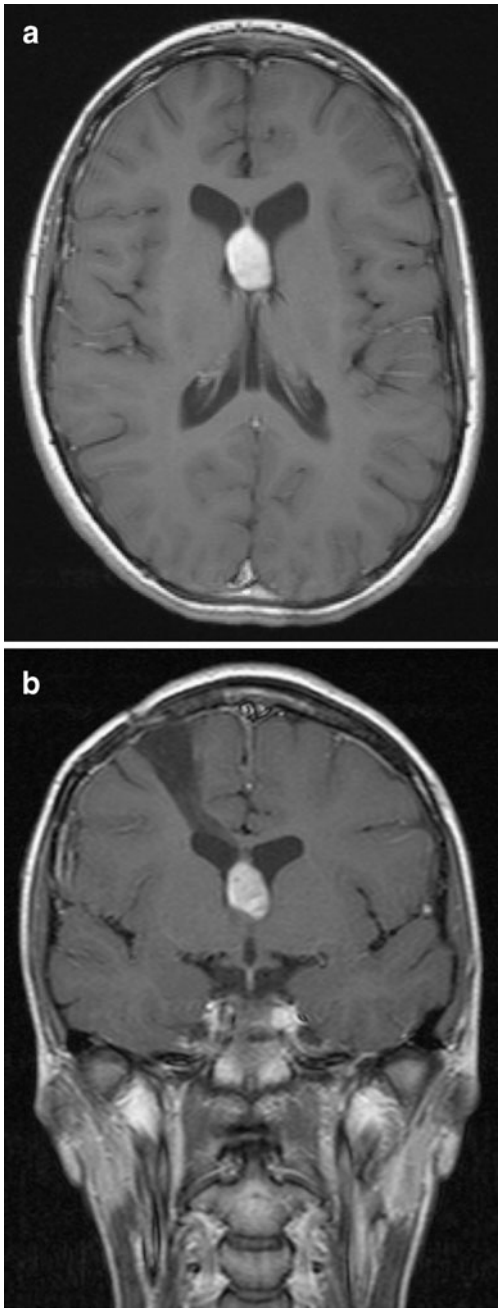

Fig. 8 **a** & **b** Contrast-enhanced MRI images in axial (**a**) and coronal (**b**) planes showing the residual tumor 3 years post surgery, which was reported to have reduced slightly compared with the first post-operative scan

0.1 to 2.5 cm^3) at a mean of 21 months (range 3–49 months) [46]. Although one might question the certainty of the smallest lesion at 0.1 cm^3 as being residue, it was concluded that residual tumors with a smaller post-operative volume had a reduced risk of progression. Gunny et al., in a series of 83 low-grade cerebellar astrocytomas, including 13 with incomplete resection, did not find statistically significant independent variables (symptomatology, age, gender, histological grade, or the Ki-67 fraction) as predictors of spontaneous regression [23]. The numbers involved were too small to assess statistical significance of the independent variables, but interestingly, tumor progression did not occur in children with residual tumor volumes below 10 cm^3. However, we have seen progression in PA tumor residuals with initial volumes lower than 10 cm^3.

The mechanism for tumor regression is not known, and is unlikely to be the same for every patient and tumor. Suggested causes include ischemic tumor necrosis from vessel occlusion, inhibition of angiogenesis, immunologic

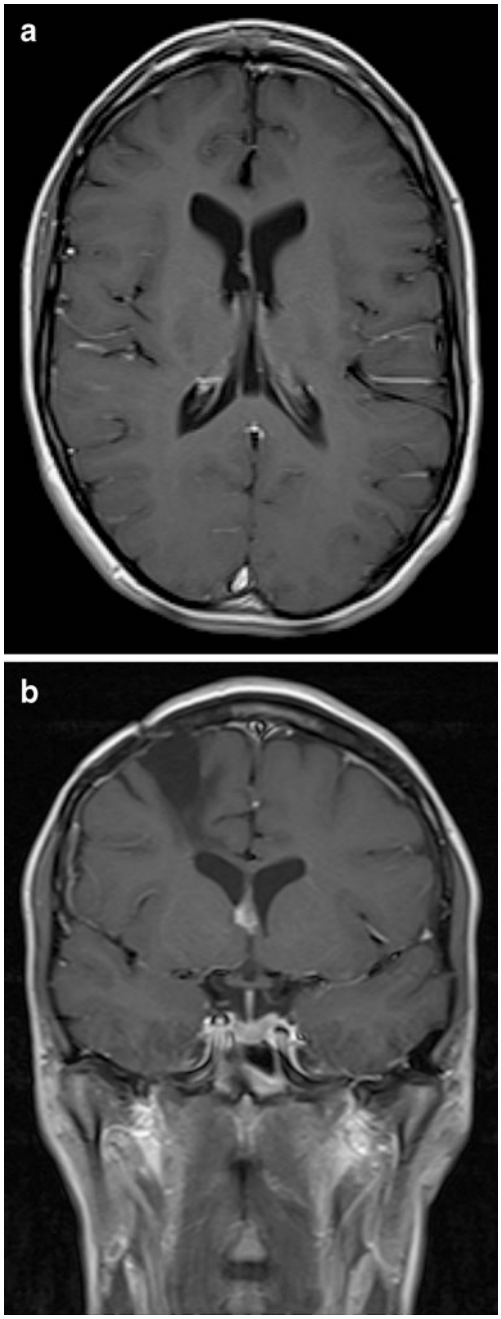

Fig. 9 **a** & **b** Contrast-enhanced MRI images in axial (**a**) and coronal (**b**) views show further regression and almost complete disappearance of the tumor remnant

factors, effects of growth factors and/or cytokines, hormonal factors, elimination of a carcinogen, psychological mechanisms, apoptosis and loss/destruction of the crucial (to tumor growth) stem cell population during the initial surgery [8, 32, 38, 49]. In our cases, the tumor remnants did not regress for the first 3 years after surgery. Therefore, the mechanisms are unlikely to be those that are initiated or augmented by surgery, e.g., vascular injury to the tumor, exposure of hidden tumor antigenic sites causing enhanced auto-immunity [15]. Regarding the possible association with hormonal changes, the onset of menarche occurred at 12 years of age, which was after surgery in case 1, and at 13 years of age and prior to surgery in case 2. The onset of menarche and rise in female hormones causing tumor regression may be a factor in our cases. There is evidence for the protective role of estrogens and other steroid hormones against gliomas, with 1.5 times higher rates of incidence of gliomas in men compared to women [30, 53]. There are reports of changes in incidence of gliomas around menarche and menopause [31, 35], and presence of hormone receptors in glial tumors [21]. A case–control study showed decreased incidence amongst women who use hormones during menopause [30], and another showed lower risk of gliomas in women that had ever been pregnant compared to never pregnant. The decreased risk increased with the number of pregnancies [53]. A rise in estrogens as a cause of tumor regression in our patients is possible, although menarche occurred more than 3 years prior to the beginning of any radiological regression in both patients.

Many patients and the families of patients with tumors aim to make significant beneficial lifestyle and dietary changes. Whether or not such dietary changes have any significant positive influence on regression of gliomas is difficult to prove or disprove. However, it has been estimated that 30–40% of all cancers can be prevented by lifestyle and dietary measures alone [18]. Obesity, concentrated sugars, refined flour products, low fiber intake, consumption of red meat, and imbalance of omega-3 and omega-6 fats all contribute to excess cancer risk, whereas intake of flax seed, abundant portions of fruits and vegetables may lower cancer risk. Allium and cruciferous vegetables are especially beneficial, with broccoli, cauliflower, and brussel sprouts being the densest source of sulforophane and rich in 3,3- diindolylmethane (DIM), which has been implicated in anti-prostate [4], breast [28], and pancreatic [1] cancer effects. Garlic is used for many benefits including its anticancer effects [5, 13, 47], the implicated constituents including Ajoene [33], Alk(en)yl sulfides [5, 45], and Gamma-glutamyl-Se-methylselenocysteine (GGMSC)[19]. The Chinese herbs, containing camptothecin and hydroxycamptothecin; harringtonine and homoharringtonine; colchicine and colchicinamide; curzerenone; monocrotaline; lycobetaine; oridonin; indirubin; cantharidinare, are thought to have a positive anticancer effect [29]. Bioactive polysaccharides occur extensively in traditional Chinese medicine, and are seen as useful adjuvant therapy in cancer therapies [12]. Other protective elements in a cancer prevention diet are thought to include selenium, folic acid, vitamin B-12, vitamin D, chlorophyll, and antioxidants such as the carotenoids (alpha-carotene, beta-carotene, lycopene, lutein, cryptoxanthin) [18]. However, the degree of impact of the myriad possible factors in causing regression of low-grade pilocytic astrocytomas is almost

impossible to ascertain. Maybe it is simply best accepted that diet, lifestyle, environment, and psychological factors can influence tumor regression.

One factor that has not been previously considered as a cause for "spontaneous" tumor regression is the use of *Cannabis*. In both of our patients, *Cannabis* use coincided with the regression of the tumors, and one must question if it had a role in the regression. *Cannabis* is mostly derived from the female plant of *Cannabis Sativa* which is an annual, dioecious flowering herb. The psychoactive constituent is 9-tetrahydrocannabinol (THC) [3]. A variety of strengths and preparations can be obtained, with the THC content being highest in the flowering tops, declining in the leaves, stems, and seeds of the plant. Marijuana (THC content 0.5–5%) is made by drying the flowering tops and leaves, hash (THC content 2–20%) is dried *Cannabis* resin, while hashish oil contains between 15% and 50% THC [3]. *Cannabis* is mostly smoked as it is the easiest way to obtain the psychoactive effects [27]. A typical joint contains between 0.5 and 1.0 g of *Cannabis*. The THC content varies between 20% and 70%, with 2–3 mg of the bioavailable (varying between 5% and 24%) THC, producing the desired effect, or "High" in occasional users. Regular users may smoke several such joints in 1 day [3, 27]. No details were available on the type, strength, and amount of *Cannabis* consumed by our two patients, except for the frequency and comments that it was generally of "High Quality" and "Powerful stuff".

Although there have been no reported deaths related to *Cannabis* toxicity [27], the acute undesirable side effects include drowsiness, anxiety, depression, palpitations, impaired reaction time, and motor skills with major implications for driving and work-related activities [3, 27]. The chronic side effects include damage to the respiratory system, impairment of reproductive function, psychosis (in large doses), and possible association with schizophrenia [36, 51]. However, there is increasing recognition of the possible benefits of the constituents of *Cannabis*, namely cannabinoids.

Cannabinoids refers to a group of compounds that are found in *Cannabis*, that are structurally or pharmacologically similar to THC and bind to the cannabinoid receptors. Around 70 different cannabinoids have been isolated; their receptors are classified as the central CB1 receptors and the peripheral CB2 receptors. CB1 is primarily found in the brain (basal ganglia and limbic system), and CB2 is almost exclusively found in the immune system, with highest concentration in the spleen [25]. There are three broad types of cannabinoids; the plant derived, such as THC and cannabidiol; endogenous cannabinoids, otherwise known as endocannabinoids (e.g., anandamide and 2-arachidonoylglycerol), which are produced in the bodies of man and animals; and synthetic cannabinoids (e.g., WIN-55, 212-2, JWH-133), which are developed in the laboratory [43].

Initial reports more than 30 years ago suggested that cannabinoids could inhibit tumor growth and prolong survival of mice with Lewis lung adenocarcinoma [25]. Subsequently, it was found that cannabinoids inhibit growth of tumor cells in gliomas and also in breast, lung, lymphoma, pancreas, and prostate cancer cells [10, 11, 24, 34, 42, 43]. In gliomas, it is thought that cannabinoids induce cell death by an apoptotic mechanism [41] and also by inhibition of tumor angiogenesis [52]. Studies using animal models demonstrated that local administration of THC or WIN-55 reduced the size of tumors that were generated by intracranial inoculation of C6 glioma cells in rats. This led to complete glioma eradication and prolonged survival in one third of the rats that were treated with these cannabinoids [22]. Administration of THC, WIN-55, 212-2 or JWH-133 decreased the growth of tumors derived from the rat glioma C6 cell line and also from GBM cells obtained from tumor biopsies of patients [22, 40]. A phase I trial, involving treatment of nine patients with recurrent glioblastoma multiforme and intratumoral injection of THC, showed a fair safety profile and anti-proliferative action on tumor cells [26].

There are encouraging prospects for the use of plant isolated cannabinoids or synthesized groups in conjunction with conventional chemotherapy. These can be administered using non-invasive routes, and have been considered in the treatment of newly diagnosed tumors [52].

In the light of the low toxicity of *Cannabis* and cannabinoids relative to many conventional cancer chemotherapeutic agents, more research may be appropriate to investigate the therapeutic use of these substances. Such research will be difficult to achieve, because *Cannabis* is considered illegal in many jurisdictions. The use of cannabinoids, either natural or synthetic, may bypass some of the social/ethical issues and may allow better-dose quantification. However, ingestion of synthesized components of an herb or food often does not have the same benefits or effects as ingesting the actual herb or food product. There may be a synergy of action of the different components of the food product, which is difficult to mimic by extracting what are thought to be the "active" elements. Thus, it may be preferable to study the impact of the plant *Cannabis*, since any beneficial effect may not be caused by one compound, molecule or cannabinoid alone [14, 16].

Multiple factors such as genetics, environment, diet, and lifestyle are known to be involved to various degrees in the development of a variety of tumors in various patients. Similarly, there may be a combination of factors (e.g., critical tumor mass, critical stem cell population, hormones, and exposure to the immune system), each of which with various degrees of influence may cause such tumor regression.

Conclusion

We have documented two cases of spontaneous regression of residual PA in the forniceal region and have discussed the possible role of *Cannabis* inhalation in promoting the regression. Based on our experience, and the increasing recognition of spontaneous regression of PA in other locations, we advise caution against further aggressive surgery or adjuvant therapy for small residuals of PAs, especially in eloquent locations. Slight progression of the residual tumor should not necessarily be an indication to intervene, since regression may occur later. Further research may be appropriate to elucidate the increasingly recognised effect of *Cannabis*/cannabinoids on gliomas.

Financial disclosure No financial relationships exist that are relevant to this study.

Conflict of interest statement The authors would like to declare that no conflict of interest exists.

Ethics The University of British Columbia Institutional Review Board does not require application for formal ethics approval for case reports involving three or fewer subjects. All participating subjects provided verbal and email consent prior to participation in this study, and all research activities were performed in accordance with the ethical standards of good clinical practice as outlined in the 1964 Declaration of Helsinki.

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