Case Report

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Drug-resistant schizophrenia-like psychosis associated with temporal non-anaplastic pleomorphic xanthoastrocytoma: unusual revealing symptom of a rare pathology

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Introduction and importance: Pleomorphic xanthoastrocytoma (PXA) was first described by Kepes *et al.* in 1979. Fewer than 200 cases have been reported in the literature. It generally involves the temporoparietal lobe. PXA has a favorable prognosis. The most reported clinical manifestation is epileptic seizures. Revealing psychiatric symptoms have an incidence varying from 50 to 78%. The most common symptoms encountered are anxiety disorders, depression, schizophrenia-like psychosis, cognitive dysfunction or even anorexia nervosa.

Case presentation: Here, the authors report a new case of non-anaplastic pleomorphic xanthoastrocytoma revealed by a drug-resistant schizophrenia-like psychosis in a 26-year-old male patient known with epileptic seizures in whom these two pathologies were intertwined and had been evolving for 5 years. The postoperative course was uneventful, and positive symptoms of schizophrenia were relatively stabilized at discharge.

Clinical discussion: Given the superficial hemispheric location of PXA, the most common clinical presentation is seizures. Psychiatric symptoms revealing brain tumors have an incidence varying from 50 to 78%. Most of these symptoms concern frontal and limbal tumors. In their case, the tumor was located in the right temporal lobe. Surgery was performed and postoperative course was uneventful even though there are conflicting reports regarding the importance of the surgical excision quality.

Conclusion: PXA remains a rare and benign primary CNS tumor. Psychiatric disorders represent a rare revealing mode of this pathology, which must lead to neuroimaging in any patient carrying this type of symptoms.

Keywords: epilepsy, MRI, pleomorphic xanthoastrocytoma, schizophrenia, surgery

Introduction and importance

Pleomorphic xanthoastrocytoma (PXA) was first described by Kepes *et al.*[1] in 1979. It is a glial tumor of a low degree of malignancy; grade II according to the WHO. It is generally located in the superficial cortex, mainly supratentorial, and particularly involving the temporoparietal lobe. Such tumors are more common in children and young adults[2] and represent less than 1% of astrocytic tumors[3]. Fewer than 200 cases have been reported in the literature[3].

PXA has a favorable prognosis. However, its malignant transformation has been proposed, which may occur between 10 and 20% of cases within a period of 7 months–15 years, progressing to anaplastic PXA or glioblastoma multiforme, classified as grade III and IV, respectively, according to the WHO[4]. The most reported clinical manifestation of such type of tumor as well as other types located in the temporal lobe is epileptic seizures[1,3]. Psychiatric symptoms revealing brain tumors have an incidence varying from 50 to 78%[5]. Most of these symptoms, ~80%, concern frontal and limbal tumors[6]. The most common symptoms encountered are anxiety disorders, depression, schizophrenia-like psychosis, cognitive dysfunction or even anorexia nervosa[7].

Here, the authors report a new case of non-anaplastic pleomorphic xanthoastrocytoma revealed by a drug-resistant schizophrenia-like psychosis in a 26-year-old male patient known with epileptic seizures in whom these two pathologies were intertwined and had been evolving for five years. The postoperative course was uneventful and positive symptoms of schizophrenia were relatively stabilized at discharge.

This case report has been reported in line with the SCARE Criteria[8].

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Case presentation

We present the case of a 26-year-old right-hand dominant male patient known to have epilepsy for 5 years and followed in the adult outpatient psychiatry department and psychotherapy for 5 years for drug-resistant schizophrenia on Risperidone and sodium valproate leading to his first admission in 2023. Stable remission was obtained with a combination of 20 mg/day of olanzapine, 400 mg/day of amisulpride, and 1500 mg/day of sodium valproate. After being discharged from the hospital, the patient was non-adherent to his treatment and stopped taking it in November 2023. The current history of his illness dates back to January 2024 when he was brought by the police officers who took him into custody for verbal and physical hetero-aggression, disorganized behavior, insomnia, and treatment refusal according to his next of kin. His mental examination revealed disorganized thoughts, delusions of persecution, and third-person auditory hallucinations. There was no family history of previous brain tumor pathologies or specific psychological disorders. According to his next of kin, our patient had no prior head trauma and all symptoms progressed to apyrexia.

Upon admission, the patient's psychiatric status was assessed using the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), and the Brief Psychiatric Rating Scale (BPRS). Haloperidol was started (15 mg/day). His electroencephalogram revealed rare intermittent spikes in a right temporoparietal area with normal awake electroencephalogram showing good organization with continuity, reactivity and good posterior dominant rhythm. There were no paroxysmal abnormalities or associated focal signs. After 3 weeks of gradual increase in haloperidol doses, psychotic symptoms worsened. Haloperidol was switched to olanzapine (20 mg/day), and amisulpride was associated (800 mg/day). Unfortunately, most symptoms did not improve, and our patient was diagnosed with treatment-resistant schizophrenia. For this reason, a first non-enhanced brain CT scan (Fig. 1) was performed showing a right temporal lesion of heterogeneous density harboring small calcifications. Further investigation by MRI (Fig. 2) showed the unique, cortical and multi-loculated right temporal lesion producing the soap bubble appearance and measuring 27×25 mm in axial plane. This lesion had a peripheral isosignal component on T1- and T2-weighted sequence and, which enhanced intensely after gadolinium chelate administration. There was no significant edema all around and the diffusion-weighted sequence did not show clear hyperintensity. All these features were in favor of a classic dysembryoplastic neuroepithelial tumor.

After informed consent from our patient and his legal guardian, excision surgery was performed in a classic supine position through a right temporal bone flap centered on the tumor. Intraoperatively, this tumor mass was friable with yellow-buff appearance containing areas of irregular calcifications (Fig. 3). Towards the end, excision was non-hemorrhagic and macroscopically complete. The postoperative course was uneventful, and our patient was referred back to his psychiatry department and psychotherapy for further management. He was assessed 4 day postoperatively, during which he did not receive his antipsychotics. The same psychotic symptoms persisted, and his usual prior treatment was resumed. When he was interviewed again after one week, he reported a decrease in auditory hallucinations. His family members reported that he was no longer aggressive towards them and he was fully adherent to treatment.

HIGHLIGHTS

- Pleomorphic xanthoastrocytoma is a low-grade astrocytoma with a favorable prognosis after total surgical resection.
- Although the location is usually supratentorial in most cases and particularly involves the temporoparietal lobe, it has also been reported in the cerebellum, cervical and thoracolumbar cord, retina, hypothalamus, thalamus, corpus callosum, pineal gland, sella turcica and brain stem.
- The most common clinical presentation is seizures. Psychiatric symptoms revealing brain tumors have an incidence varying from 50 to 78%. Most of these symptoms, ~80%, concern frontal and limbal tumors. The most common symptoms encountered are anxiety disorders, depression, schizophrenia-like psychosis, cognitive dysfunction or anorexia nervosa.
- Radiologically, PXAs present as well-circumscribed superficial tumors with dual components, solid and cystic, with leptomeningeal contact.
- PXA is a benign astrocytic tumor (WHO grade II) that presents as a solid and cystic superficial mass. Tumor cells are either spindle-shaped with elongated nuclei or large round cells with a single or multilobulated nucleus or multiple nuclei. In immunohistochemistry, PXA is positive for GFAP, S100 protein, vimentin, reticulin and Periodic acid-Schiff and negative for EMA and synaptophysin.
- Concerning therapeutic management, no formal guidelines have been reported and there are conflicting reports regarding the importance of the surgical excision quality.
- As for radiotherapy, there is little data for its use. Some reports have mentioned an association with its use postoperatively and the shorter progression-free improvement.

On histopathology (Fig. 4) the specimen cells were pleomorphic, spindle-shaped, round mononucleated or giant multinucleated. Their nucleus was large, hyperchromatic with prominent nucleus or often eosinophilic pseudoinclusions. Some nuclei were monstrous hyperchromatic. Mitoses were estimated at 3 M/10 per high-power field. The cytoplasm was abundant eosinophilic or often clear microvacuolar (xanthomatous in appearance). There were quite numerous intra- or extra-cytoplasmic eosinophilic bodies with moderate lymphoid infiltrate without obvious necrosis or microvascular proliferation. On immunohistochemical assessment, tumor cells were positive for the glial fibrillary acidic protein (GFAP), CD34, S100 protein and for OLIG2 and negative for synaptophysin and keratin. There was no loss of INI1 expression and the Ki-67 proliferation index was estimated at 42%. All these histological data were in favor of a cerebral pleomorphic xanthoastrocytoma grade 2 according to WHO 2021.

Clinical discussion

Pleomorphic xanthoastrocytoma is a low-grade astrocytoma, with a favorable prognosis after total surgical resection[2]. PXA in

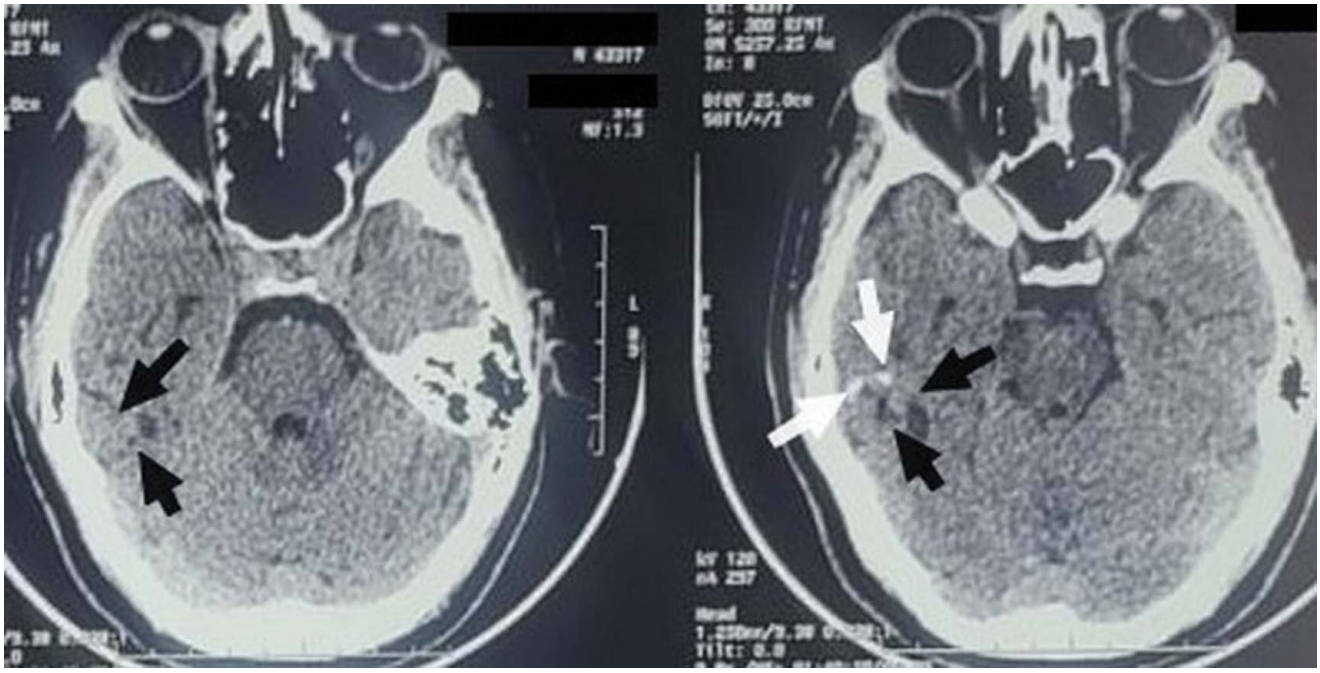

Figure 1. A non-enhanced brain computed tomography scan in axial plane and parenchymal window showing a right temporal lesion of heterogeneous density (black arrows) harboring small calcifications (white arrows).

its anaplastic and benign form affects middle-aged patients according to She *et al.*[9], with a mean age of 47.7 years at the time of diagnosis. In 2004, Tekkõk and colleagues reported 200 cases of PXA over a 25-year period; a subsequent study in 2007 recorded 40 additional cases[10]. Yu *et al.*[11] added 84 patients more recently. From the grouped analysis of these series, it may be defined that PXA is a tumor of young patients, with its peak incidence between 10 and 30 years of age. Our patient was in the range as he has 26 years old. There is no difference between the sexes in terms of frequency[12]. Although the location is usually supratentorial in most cases and particularly involves the temporoparietal lobe[3], it has also been reported in the cerebellum, cervical and thoracolumbar cord, retina, hypothalamus, thalamus, corpus callosum, pineal gland, sella turcica and brain stem[11,13]. In our case, the tumor was located in the right temporal lobe.

Given the superficial hemispheric location of PXA, the most common clinical presentation is seizures[1,3], an event that has been reported in 70% of patients[14], so much so that many of them have a history of epilepsy months or years before diagnosis. This was described in our patient who was known with epileptic seizures years before tumor diagnosis. Other clinical manifestations include focal neurological deficit, altered vision, headache and occasionally intracerebral hemorrhages[11]. Psychiatric symptoms revealing brain tumors have an incidence varying from 50 to 78%[5]. Most of these symptoms, ~80%, concern frontal and limbal tumors[6]. The most common symptoms encountered are anxiety disorders, depression, schizophrenia-like psychosis, cognitive dysfunction or anorexia nervosa[7]. In 2018, Oladiran *et al.*[15] published a case of an anaplastic temporal PXA presenting with a musical hallucination in a 28-year-old patient. One year ago, De Maeseneire *et al.*[16] reported a case of left temporo-insular glioma revealed by musical hallucinations. Auditory hallucinations in our case were not musical but rather third-person auditory hallucinations. Generally speaking, tumor location remains the key to such association of this kind of psychiatric symptoms. However, some studies reported in the literature noted personality changes and emotional lability in lesions located outside the frontal lobe or even in the limbic system[17]. In 2015, Madhusoodanan *et al.*[18] conducted a meta-analysis carried out on 148 cases of tumors with psychiatric symptoms, including 12 case series, 22% of cases presented psychiatric symptoms and the most affected locations were the cerebral cortex, the pituitary gland, the pineal gland and finally the posterior cerebral fossa. In 2016, Landais *et al.*[19] reported a series of 10 consecutive patients with temporal dysembryoplastic neuroepithelial tumors, 5 of whom had interictal psychiatric disorders. Their patients were distributed as follows: one case of undifferentiated schizophrenia, two cases of "borderline" personality, one case of unspecified personality disorder with mythomania and finally one case of intermittent explosive disorder with mild mental retardation. In our patient, verbal and physical hetero-aggression, disorganized behavior and insomnia were noted. Mental examination revealed disorganized thoughts, delusions of persecution, and third-person auditory hallucinations.

Radiologically, PXAs have certain characteristics reminiscent of high-grade gliomas. In most cases, they present as well-circumscribed superficial tumors with dual components, solid and cystic, with leptomeningeal contact[20]. This cystic component is hypodense on CT while the solid component is generally hypo to isodense and may even be hyperdense, with calcifications. There is often an enhancement of the solid component as well as the cyst's wall after iodine-based contrast material injection[20]. In our patient, the tumor was of heterogeneous density (hypo and isodense) harboring small calcifications. On MRI, the solid

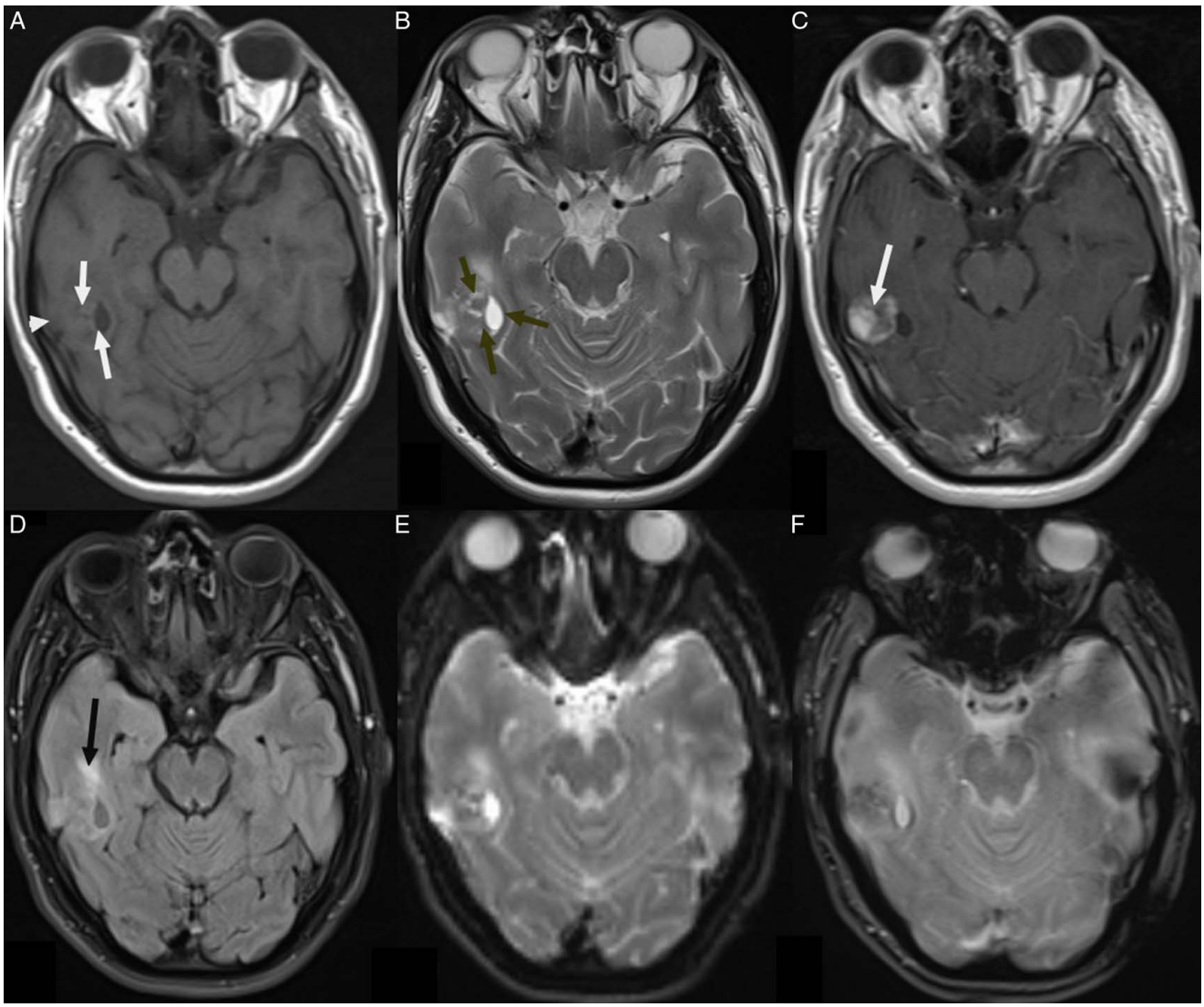

Figure 2. Axial brain enhanced MRI showing unique, cortical and multi-loculated right temporal lesion producing the soap bubble appearance [(A) white arrows] [(B) black arrows] and measuring 27 × 25 mm in axial plane. The lesion had peripheral isosignal component on T1- and T2-weighted sequence (A, B, respectively) and enhances intensely after gadolinium chelate administration [(C) white arrow]. Note a minimal edema all around on T2-weighted-fluid-attenuated inversion recovery sequence [(D) black arrow]. Diffusion-weighted sequence did not show clear hyperintensity (E) and the gradient echo sequence revealed no bleeding (F).

component is isointense on T1-weihted image and hyperintense on T2-weihted sequence with heterogeneous enhancement after gadolinium chelate injection with peripheral rim enhancement of the cyst. The cystic contents may be either isointense or hyperintense relative to the cerebrospinal fluid depending on the imaging sequence used[20]. Sometimes, around the lesion, a minimal amount of vasogenic edema may be seen. Inconsistent leptomeningeal enhancement may be reported[21,22]. In our patient, the lesion was cortical and multi-loculated producing the soap bubble appearance. It had a peripheral isosignal component on T1- and T2-weighted sequence and enhanced intensely after gadolinium chelate administration. There was no significant edema all around as it was described in the literature.

On angiography, the PXA is hypovascular[23]. On fluorodeoxy glucose positron emission tomography, there is fairly high glucose metabolism associated with hypoperfusion on SPECT perfusion scans[24]. We did not perform these techniques for lack of means.

As for its macroscopic and histological description, PXA is a benign astrocytic tumor (WHO grade II) that presents as a solid and cystic superficial mass and that may reach the leptomeninges. PXA is most often located in the temporal lobe as in our patient. The main histopathological description was reported for the first time by Kepes *et al.*[1] after microscopic examination of 12 cases with almost identical features. Kepes mentioned moderate cellularity and predominantly pleomorphic with foci of lymphoplasmacytic infiltration as described in our patient. There was no necrosis and rare mitoses have been noted[1,14,25,26]. In our patient mitoses did not exceed 3/10 per high-power fields. Tumor cells are either spindle-shaped with elongated nuclei or large round cells with a single or multilobulated nucleus or multiple nuclei as seen in our case. These cells invade directly into healthy brain parenchyma or into perivascular spaces[27]. As for the

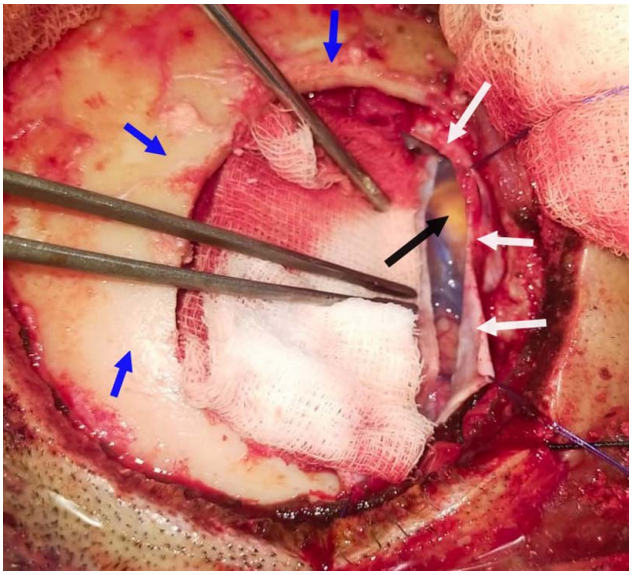

Figure 3. Intraoperative view showing, through the temporal bone flap (blue arrows) and after dura opening (white arrows), the tumor mass with yellow-buff appearance (black arrow).

cytoplasm, it is eosinophilic harboring hyaline proteins and lipids. In immunohistochemistry, it is positive for glial fibrillary acidic protein (GFAP) like our case. This positivity varies depending on its lipid content[25]. PXA are also positive for S100 protein, vimentin, reticulin and Periodic acid-Schiff and negative for epithelial membrane antigen (EMA) and synaptophysin as described in our patient. Note that a unique histopathological form with an abundant clear cellular component and focal papillary appearance may also be noted[28], something which was not encountered in our patient. Malignant transformation (WHO grade III) is defined by the onset of necrosis associated with high mitotic activity, generally greater than 5 mitoses/10 high-power fields (HPF), and increased cellularity, which was not seen in our patient. Ependymoma-like pseudorosette formation and focal endothelial proliferation have been reported[29,30].

Concerning therapeutic management, and due to the rarity of the pathology, no formal guidelines have been reported[20]. There are conflicting reports regarding the importance of surgical excision quality[31]. However, several reports have mentioned it as a reliable prognostic factor for short progression-free and overall survival[14,32], with gross total resection correlating with a 10-year overall survival of 82%[33]. According to most authors and as standard practice, gross total resection should be the ultimate goal of the surgeon if it is feasible and without neurological complications[20]. This was our therapeutic behavior from the beginning.

As for radiotherapy, there is little data for its use. Some reports have mentioned an association with its use postoperatively and shorter progression-free improvement[25,34]. However, no definitive improvement in overall survival has been demonstrated. The use of doses varying between 45 and 54 Gy as adjuvant or salvage treatment seems reasonable, with or without concomitant chemotherapy given the lack of data. In many reports, earlier use of radiotherapy after subtotal surgical resection (and/or anaplastic PXA) may be indicated given the poorer results associated with these factors. Craniospinal irradiation is indicated in cases of leptomeningeal spread at initial diagnosis or in cases of tumor recurrence[35–37]. In our patient, we decided not to perform radiotherapy as tumor surgical removal was complete and there were no signs of anaplasia on histopathology.

The combination of traditional chemotherapy is generally not very effective or even ineffective as adjuvant treatment[14,25]. However, when surgical resection or radiotherapy is not a viable option or when the disease progresses, this systemic option can be used[20].

Through this report, we have contributed to enriching the existing literature with more details, with a new rare case of fairly rare neoplastic pathology of the central nervous system affecting the middle-aged patients and having fairly rare revelation by schizophrenia-like psychosis symptoms. We emphasize the need to perform brain imaging in any patient who presents with such type of symptom, especially if there is another associated neuropathy such as epilepsy.

Conclusion

PXA remains a rare and benign primary CNS tumor. Its cerebral location determines its usual revealing clinical signs. However, psychiatric or psychological disorders including schizophrenia-like psychosis represent a rare revealing mode of this pathology, which must lead to neuroimaging in any patient carrying this type of symptoms. In this way, there is a greater probability of

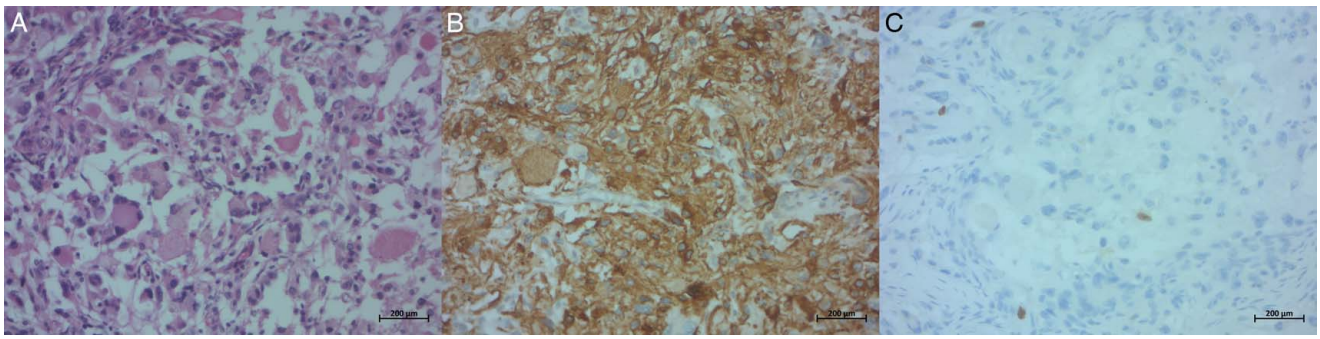

Figure 4. Histological findings of the specimen showing nuclear pleomorphism with xanthomatous cells Eosinophilic bodis [(A) hematoxylin and eosin200 ×], glial fibrillary acidic protein expression in large pleomorphic cells [(B) 200 ×] and immnoreactivity for Ki-67: 2% [(C) 200 ×].

achieving an early diagnosis and timely neurosurgical treatment in conjunction with psychiatric treatment if necessary.

Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Author contribution

All authors contribute to write this manuscript.

Conflicts of interest disclosure

The authors declared no potential conflicts of interests with respect to research, authorship and/or publication of the article.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Mehdi Borni.

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Patient perspective

During hospitalization and at the discharge, the patient has given the opportunity to share their perspectives on the intervention the boy received and she was satisfied with the care.

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