RAISED INTRACRANIAL PRESSURE IN AN ADULT PATIENT REVEALS A VENTRICULAR NEURONAL-GLIAL TUMOUR: A CASE PRESENTATION AND SHORT REVIEW OF LITERATURE

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Abstract

We present a very rare case of a middle-aged female who presented with clinical and radiological signs of elevated intracranial pressure that was non-responding despite double external ventricular drain. An explorative ventricular endoscopy appealed a tumor which partially obstructed the foramen of Monroe. Immunohistochemical tests showed that tumor cells were positive for synaptophysin, Glial Fibrillary Acidic Protein (GFAP) and focally for CD99 while they were negative for CD20, TTF1 and CK CAM. The Ki67 profileration marker was measured at approximately 70%. Thus, the morphological image and immune phenotype of the tumor were compatible with Primitive Neuroectodermal Tumor (PNET). Molecular analysis showed no MGMT methylering of mutation showed in TP53, IDH1, hTERT promoter and the picture was associated with glioneuronal tumor. The patient was diagnosed with an embryonal tumor with multilayered rosettes. According to our knowledge, the location of this type of tumor is very uncommon and less than 5 cases have been described according to a short review of literature.

Key words: leptomeningeal contrast enhancement, PNET, NOS, ventricular embryonal central nerve system tumor

ΑΥΞΗΜΕΝΗ ΕΝΔΡΟΚΡΑΝΙΑ ΠΙΕΣΗ ΣΕ ΕΝΗΛΙΚΑ ΑΣΘΕΝΗ ΑΠΟΚΑΛΥΠΤΕΙ ΕΝΑΝ ΕΝΔΟΚΟΙΛΙΑΚΟ ΓΛΟΙΟΝΕΥΡΩΝΙΚΟ ΟΓΚΟ: ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΣΤΑΤΙΚΟΥ ΚΑΙ ΣΥΝΤΟΜΗ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΒΙΒΛΙΟΓΡΑΦΙΑΣ

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Περίληψη

Παρουσιάζουμε μια πολύ σπάνια περίπτωση μεσήλικης γυναίκας με κλινικά και ακτινολογικά σημεία αυξημένης ενδοκράνιας πίεσης και μη ικανοποιητική ανταπόκριση παρά τη διπλή εξωτερική κοιλιακή παροχέτευση. Κατά τη διενέργεια διερευνητικής ενδοσκόπησης του κοιλιακού συστήματος παρατηρήθηκε όγκος ο οποίος απόφραζε μερικώς το τρήμα του Monroe. Οι ανοσοϊστοχημικές εξετάσεις ανέδειξαν καρκινικά κύτταρα θετικά στην συναπτοφυσίνη, Glial Fibrillary Acidic Protein (GFAP) και εστιακά για CD99 ενώ ήταν αρνητικά για CD20, TTF1 και CK CAM. Ο δείκτης Ki67 μετρήθηκε περίπου στο 70%. Έτσι, η μορφολογική εικόνα και ο ανοσοποιητικός φαινότυπος του όγκου ήταν συμβατοί με το Primitive Neuroectodermal Tumor (PNET). Η μοριακή ανάλυση δεν ανέδειξε MGMT μεθυλίωση της μετάλλαξης στους προαγωγείς TP53, IDH1, hTERT και η εικόνα συσχετίστηκε με γλοιονευρωνικό όγκο γνωστό και ως περιφερικό νευροεξωδερμικό όγκο (PNET). Η ασθενής διαγνώστηκε με εμβρυϊκό όγκο με πολυστρωματικές ροζέτες. Σύμφωνα με τις γνώσεις μας, η εντόπιση αυτού του τύπου όγκου είναι πολύ σπάνια εντός του κοιλιακού συστήματος και έχουν περιγραφεί λιγότερες από 5 περιπτώσεις σύμφωνα με μια σύντομη ανασκόπηση της βιβλιογραφίας.

Λέξεις-κλειδιά: λεπτομηνιγγική πρόσληψη σκιαγραφικού, PNET, NOS, ενδοκοιλιακός εμβρυικός όγκος ΚΝΣ.

Introduction

Raised intracranial pressure (ICP) is a clinical condition associated with an elevation of the pressures within the cranium with a level more than 20 mm Hg [1]. The mmHg value is multiplied by 1.36 to determine the equivalent value in cm H_20. The clinical suspicion of high ICP could be raised with the following usual clinical signs: headaches, visual changes, nausea and/or vomiting, altered level of consciousness varying from somnolence to coma and optic disc edema. The causes of high ICP can be divided in intracranial (because of a hematoma, tumor, meningitis, increased production of cerebrospinal fluid (CSF) or obstruction in ventricular system, venous sinuous thromboses/stenosis, and intracerebral aneurysms, idiopathic/benign intracranial hypertension), extracranial (because of drugs, seizures and hypoventilation) and postoperative (because of vasodilation, edema of CSF disturbances) .Patients with suspected elevated ICP must undergo a computer tomography (CT) or magnetic resonance imaging (MRI) aiding to determine the cause of high ICP and exclude conditions which need emergent surgical intervention. When the ICP is too high, activation of Cushing triad is appearing, with elevation of blood pressure, bradycardia and irregular respiration, caused by brain herniation [2] . The diagnosis and management of elevated ICP requires expertise and patients appearing with these symptoms need placement of invasive monitoring devices such as external ventricular drain (EVD) [3]. The differential diagnosis is challenging and requires multidisciplinarity and access to advanced imaging methods. Herein, we present a very rare case of a middle-aged patient who was admitted to our hospital because of clinical and radiological signs of elevated ICP , caused of a ventricular embryonal central nerve system (CNS) tumor, not otherwise specified (NOS), which was initially difficult to identify. We have also conducted a systematic review of the literature searching for similar case presentations.

Case Presentation

A 41-year-old Caucasian female, non-smoker with a bladder tumour of suspected low-malign type at the age of 39 years with objection from

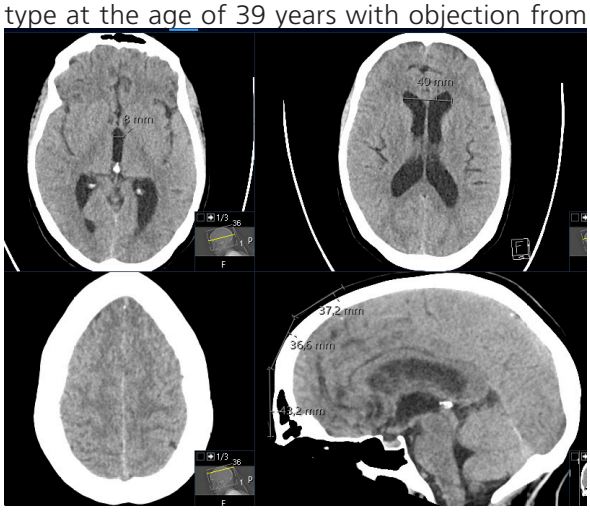

Figure 1: Initial Brain CT shows a subtle hydrocephalus with a moderate widening of the temporal horns and moderate effacement of the parasagittal sulci.

radiological controls, proceeded to the emergency room of Kalmar's hospital, Sweden, because of slight progressive headache during the past 3 months with changing intensity the last week combined with nausea and transient diplopia. Neurologist and Neurosurgeon in University hospital of Linkoping were contacted because of aggravated neurological status with progressive consciousness disorder and suspected dysphasia, diplopia and vomiting. The brain CT showed increased ICP and hydrocephalus (figure 1), why she was immediately admitted to our hospital. The patients' systolic pressure had a maximum to 150 mm Hg and telemetry showed episodes with bradycardia. Arterial blood gases showed a pH 7.52, pCO_2 4.1 and pO_2 22.8. The neurological status revealed anisocoria with bilateral pupillary light-near dissociation and Glasgow Coma

Scale 3. A new brain CT showed depression of 3rd ventricle's floor, crowding of the sulci superiorly and hydrocephalus. An acute operation with right sided external ventricular drain (EVD) was performed and yellow-coloured cerebrospinal fluid (CSF) came in the drainage system while the intracranial pressure was around 28 cm H_20.

The patient admitted to the neurosurgery intensive care department with continuous electroencephalography (EEG). During the wake-up attemption vertical nystagmus and tonic-clonic seizures were observed and short episodes of spike and waves discharges followed by low activity about 6-7 Hz in the right hemisphere were noticed in the

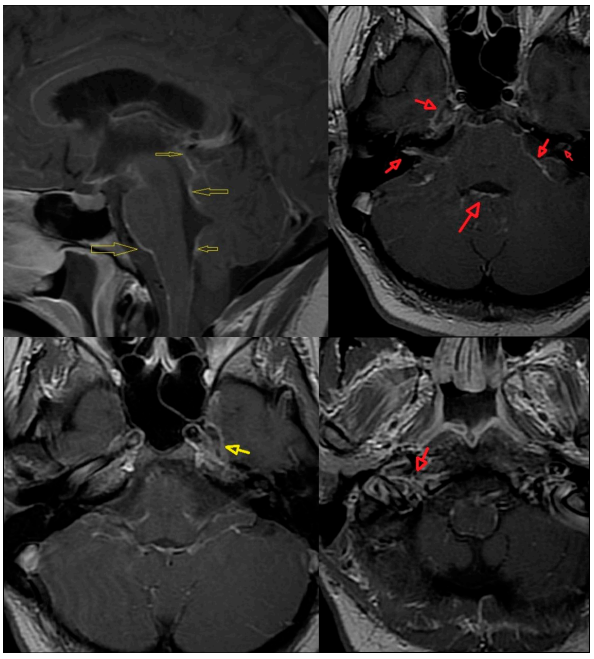

Figure 2: Brain MRI with gadolinium-based contrast agent shows a widespread leptomeningeal contrast enhancement on the surface of the brain supra- and infratentorial as well as intraventricular ependymal contrast enhancement and engagement of the cranial nerves. MRI with gadolinium-based contrast agent shows widespread contrast enhancement of the subarachnoid space in the spinal canal. T1WI on left, T1GDWI on the right.

EEG. Levetiracetam and fenytoin infusion were administrated with good effect. The postoperative brain CT showed regression of both the cerebral oedema and hydrocephalus.

A brain Magnet Resonance Imaging (MRI) with gadolinium-based contrast agent, at day two, showed a widespread leptomeningeal contrast enhancement on the surface of the brain supra- and infratentorial as well as intraventricular ependymal contrast enhancement and engagement of the cranial nerves (figure 2). No tumour suspicion found in the cerebral parenchyma. A whole spine MR with gadolinium-based contrast agent showed widespread contrast enhancement of the subarachnoid space in the spinal canal (figure 2). In addition, at Th11 level there was an intramedullary 5 mm large charge adjacent to a more than 1 cm large cyst-like medullary wool expansivity with slightly surrounding medullary edema. A contrast thoracic and abdominal CT, compared with the previous one from two years ago, showed no tumours or other abnormalities of interest. Transthoracic and transesophageal echocardiography were normal.

The CSF albumin was elevated to 4140 mg/L (normal <320 mg/L) (20 samples, median 4275, range 906-8950 mg/L) without intrathecal production of immunoglobulin bands. Blood samples including erythrocyte sedimentation, liver status, angiotensin converting enzyme (ACE), creatinine kinase, thyroid status, cortisol, adrenocorticotropic hormone, protein electrophoresis, antinuclear antibodies, anti-neutrophil cytoplasmic antibody, immunoglobulin 4 and screening tests for syphilis, tuberculosis, hepatitis A, B and C antibodies, mycoplasma pneumonia antibodies, syphilis antibodies, herpes simplex antibodies, human immunodeficiency virus, Borreliosis, mycobacteria culture, herpes simplex virus, human T-lymphotropic virus, varicella zoster virus, enterovirus, tick-borne encephalitis, toxoplasma and entamoeba histolytica were normal. Meanwhile, the patient operated with new EVD bilaterally, because of continuous dysfunction.

CSF cytology was performed 10 separate times showing high concentration of lymphocytes and granulocytes without any malignancy cells while CSF leucocytes were initially normal. Flow cytometry analysis of the CSF showed lymphocytes at the level of 10% of all cells and cluster of differentiation (CD) 4/CD8 was near to 2/1.

Neurosarcoidosis was considered as a probable explanation but the CD4/CD8 ratio was not compatible with the diagnosis, usually over 5/1 [4]. Paraneoplastic antibodies for glutamic acid decarboxylase, anti-glutamate receptor, anti-N-methyl-d-aspartate receptor, leucine-rich glioma-inactivated 1, γ-aminobutyric acid-B receptor, dipeptidyl-peptidase–like protein, contactin associated protein 2, amphiphysin, CV2, Hu, MA, Ri, purkinje cell, glutamic acid decarboxylase 65-kilodalton isoform, recoverin, anti-glia nuclear, Zic4, titin, aquaporin 4 and 1, myelin oligodendrocyte glycoprotein, were not identified. Furthermore, CSF ACE was elevated to 7.2 (normal <2.0 E/L). Initially, after consultation with infectious disease specialist, treatment with acyclovir and meropenem was started.

A new brain MRI with contrast, one week after the first one, showed progress of the leptomeningeal enhancement without signs of venous sinus thrombosis, vasculitis and malignancy.

During the third week and due to the continuous need of CSF drainage, brain biopsy was obtained from the frontotemporal region of the right hemisphere. The histological examination showed leptomeningeal no granulomatous inflammatory infiltration, negative IgG4 immunostaining and no signs of malignancy. After the biopsy the patient was treated for iatrogenic meningitis effectively. Meanwhile, 4 weeks after admission to our hospital because of continuous right EVD dysfunction the patient operated with bilateral EVD. Under EVD noticed a median of 380 ml CSF drainage (range 95-553) per day. Despite both EVDs, there were plenty of EVD- dysfunction moments where local intraventricular actilyse gave

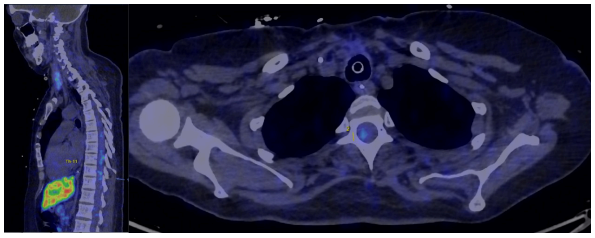

Figure 3: A body positron emission tomography (PET)/CT 68Ga-DOTATOC NET showed scattered focal radiotracer uptake along the spinal cord (cervical and Th-7 to Th-9).

effect. The ICP was stable except for these moments where the ICP was elevated up to 45 cm H20.

The diagnosis was challenging, and the patient's neurological status was worsened with slight left hemiparesis and decreased level of consciousness. A body positron emission tomography (PET)/CT 68Ga-DOTATOC NET showed scattered focal radiotracer uptake along the spinal cord (cervical and Th-7 to Th-9) (figure 3). Methotrexate, Infliximab, Solumedrol infusions as well as folic acid cure were started as primary CNS sarcoidosis was suspected. During this medication, there was observed intermittent bilateral EVD dysfunction, which answered poorly to local thrombolysis.

The patient had six surgeries in one month including an initial right sided frontal ventriculostomy, open biopsy of frontotemporal brain and meninges of the right side with no diagnostic yield, three revisions of ventriculostomies due to failure and addition of a left sided ventriculostomy. Finally, a month after admission, an explorative endoscopy was performed due to the unexplained repeated ventriculostomy blockages. In retrospect, a third ventricle mass was seen on two gadolinium enhanced T1-weighted preoperative MRI-scans.

A Storz Oi-endoscope with a zero-degree optic was used with a right frontal approach using the canal after the performed ventriculostomy. On entering the right frontal horn, it was filled out by a mass consisting of multiple reddish semi-transparent membranes through which the ependyma was visible. Following the ventricle wall the mass could be rounded and it became apparent that the mass obstructed the foramen of Monroe, filling out the posterior aspect of the 3rd ventricle and right side-ventricle. On manipulation it appeared to have an attachment in the roof of the 3rd ventricle, although this could never be visualized. The floor of the 3rd ventricle was visualized and a ventriculocisternostomy was performed with a Liljequist membrane being visualized and subsequently opened. In the prepontine CSF-spaces there were multiple inflammatory membranes obstructing CSF-flow and thus no hope of the patient being drain-independent. Returning to the level of foramen of Monroe, the mass was coagulated and cut. The component obstructing the foramen was extracted through the canal along with the free floating mass in the right side-ventricle. The left side ventricle was then explored endoscopically with an identical presentation as in the right and an even more pronounced foraminal obstruction. The remaining 3rd ventricle mass was then mobilized with forceps up through the foramen of Monroe along with the cut segment from the right side. The attachment to the roof of the 3rd ventricle was then apparent although out of sight and after some delicate traction it let go and the whole mass could be extracted and sent for pathology. No significant bleeding was seen, the endoscopy was discontinued and bilateral EVDs were reimplanted.

On postoperative imaging the following day there was a post-operative intraventricular hematoma filling out a large portion of the left side-ventricle, apparently coming from the region of the left foramen of Monroe (figure 4).

Immunohistochemical tests showed that tumor cells were positive for synaptophysin, GFAP and focally for CD99 while they were negative for CD20, TTF1 and CK CAM. The Ki67 profileration marker was measured at approximately 70%. Thus, the

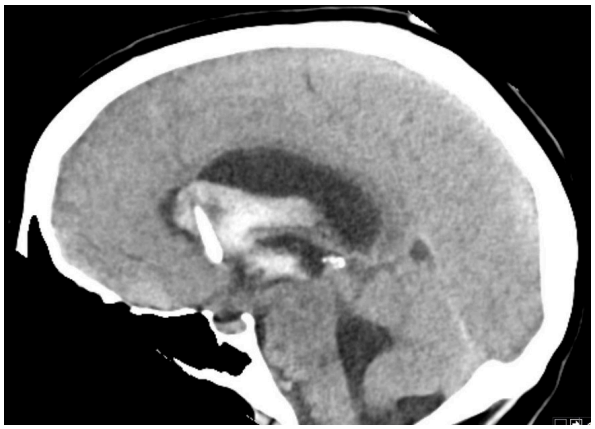

Figure 4: On postoperative imaging the following day there was a post-operative intraventricular hematoma filling out a large portion of the left side-ventricle, apparently coming from the region of the left foramen of Monroe.

morphological image and immune phenotype of the tumor were compatible with Primitive Neuro-Ectodermal Tumor (PNET). Molecular analysis showed no MGMT methylering of mutation showed in TP53, IDH1, hTERT promoter and the picture was associated with glioneuronal tumor (figure 5). After consultation with oncologists considering the poor prognosis, patient's performance, tumor location, need of continuous drainage during eventual chemotherapy and radiotherapy as well as respecting patient's autonomy and decision not to receive any treatment, we didn't proceed to any further therapeutical approach and the patient died two months after admission to our hospital.

Review of literature

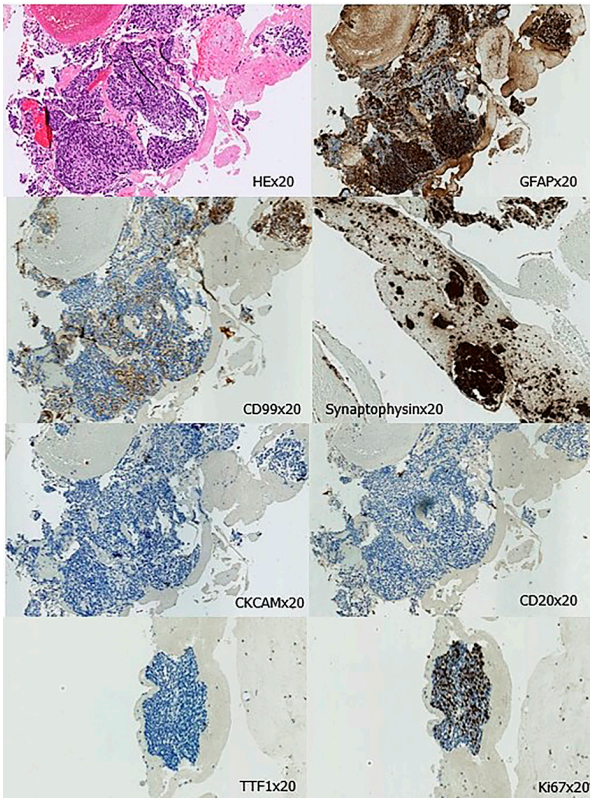

Figure 5: Immunohistochemical tests showed that tumor cells were positive for synaptophysin, GFAP and focally for CD99 while they were negative for CD20, TTF1 and CK CAM.

The incidence of PNET is 0.15 per 100000 children age 0 to 4 and only 3 per 10^6 individuals with an age 15 to 19 years [5]. A literature search was contacted in PubMed/Medline in January 2023 to identify all studies including following specific terms: (((diffuse[Title/Abstract]) OR (disseminated[Title/Abstract]) OR (leptomeningeal[Title/Abstract]) OR (multifocal[Title/Abstract])) AND ((glioneuronal[Title/Abstract]) OR (glioneural[Title/Abstract])) AND ((tumor[Title/Abstract]) OR (tumour[Title/Abstract]) OR (neoplasm[Title/Abstract]))) OR (DLGNT[Title/Abstract]) OR (((anaplastic[Title/Abstract]) OR (malignant[Title/Abstract])) AND ((glioneuronal[Title/Abstract]) OR (glioneural[Title/Abstract]))) OR (((glioneuronal tumor[Title/Abstract]) OR (glioneuronal tumour[Title/Abstract]) OR (glioneural tumor[Title/Abstract]) OR (glioneural tumour[Title/Abstract])) AND (neuropil-like islands[Title/Abstract])) OR (rosetted glioneuronal[Title/Abstract]) OR (rosetted glioneural[Title/Abstract]) OR (((rosette[Title/Abstract]) AND ((glioneuronal[Title/Abstract]) OR (glioneural[Title/Abstract]))) NOT (rosette forming glioneuronal[Title/Abstract])).

We identified 316 results. 160 results after search for rosette forming glioneuronal in title or abstract. In the whole literature we aimed to identify 2 other cases with an adult presentation of an intraventricular neuronal-glial tumor. He et al. reported a 36-year-old patient who presented with progressively worsening headache under a period of 2 months. Brain MRI showed multiple tubercula on the walls of the lateral and third ventricles. Histopathologically, a hypercellular tumor with small round cells containing hyperchromatic nuclei and a high nucleus/cytoplasm ratio was diagnosed. The tumor was positive for neuron-specific enolase (NSE), CD99, CD56, and S-100 expression and negative for Synaptophysin (Syn), Vimentin, and epithelial membrane antigen (EMA) expression. The Ki-67 index was 70%. Based on these findings, this tumor was diagnosed as an intraventricular PNET [6]. Asmoniene et al. described a rare case of a 51-year-woman applied to her family doctor with progressive vision loss, vertigo, headache and weakness in her legs lasting for two months where brain MRI showed an irregularly shaped heterogenous solid mass with strong contrast enhancement in the quadrigeminal cistern. The patient was diagnosed with a intraventricular PNET [7].

Discussion

According to our knowledge, this is a very rare case presentation of an intraventricular CNS PNET in an adult patient. The PNET terminology does not exist since the new WHO revised classification was released 2016 [8]. The clinical course, the radiological features, the histological analysis compared with the immunohistochemistry ensured the diagnosis of glioneuronal tumor. Unfortunately, a treatment strategy for PNETs has not yet been established and the difficulties in finding the diagnosis led to worseness of patient's condition.

The histological typing of tumors has been edited four times since 1979. The differences between these editions are the additional aids for definition of

brain tumors. The 2016 World Health Organization classification of tumors of the CNS introduced molecular parameters in addition to histology for definition of tumor entities [8]. Gloioblastoma with primitive neuronal component was added as a pattern in gloioblastoma which previously in the literature was described as a gloioblastoma with primitive neuroectodermal tumor PNET-like component. PNET is a primitive, undifferentiated small round cell highly malignant tumor arising from germinal matrix cells of the primitive neural tube. PNETs may occur in almost any location within or outside the central nervous system. PNETs recognized outside the CNS are diagnosed as peripheral PNETs. CNS PNET and peripheral PNET are different entities with different immunohistochemical profiles and genetic backgrounds. CNS-PNET mostly occurs in children and accounts for only 1% of primary CNS tumors. PNET occur primarily in young children; they are extremely rare in adults [9] . CNS PNETs can be divided into 2 large groups: infratentorial tumors (medulloblastoma or iPNETs) and supratentorial tumors (sPNETs). Ventricular primary PNET is extremely rare; to the best of our knowledge, less than 10 cases of have been reported in the English literatures [6]. The clinical appearance of PNETs are seizures, focal neurological deficits and increased ICP [10]. In our case the patient presented with headache caused by elevated ICP.

The radiological appearance shows in T1 gadolium markedly heterogeneous enhancement and leptomeningeal seeding is common, DWI shows often restricted diffusion Computed tomography and magnetic resonance imaging findings in primitive neuroectodermal tumours in adults.

Typically, the mass reveals a low signal intensity on T1-weighted image, and high signal intensity on T2-weighted image. The mass shows acidly enhancement after contrast MRI scan. The tumor signal is not uniform, mostly due to necrosis and cystic changes, or accompanied by hemorrhage and calcification in the tumor. Although the location of this PNET was unique, the MRI signal characteristics of this case were similar to those of tumors occurring in the brain hemisphere, such as non-peritumoral edema, and well-defined borders. One possible reason for these characteristics is that the main mechanism of PNET growth is proliferation, which is different from the infiltrative growth observed in other malignant brain tumors. The enhanced extent of the tumor was associated with the number of blood vessels in the tumor [11]. The solid composition in DWI can help identify the solid component of the tumor. In this case, the tumor had high signal in DWI and obviously enhanced, which shows more densely arranged tumor cells with a rich blood supply, which has certain significance in differential diagnosis [12].

On immunohistochemistry, PNETs are positive for neuronal or glial markers such as neuron-specific enolase, CD99, S-100, NCAM, synaptophysin, and glial fibrillary acidic protein. A study by Kampman et al. showed that expression of MIC2 glycoprotein by immunochemical staining (CD99) is helpful in differentiating central and peripheral PNET [13]. PNET is densely cellular with undifferentiated, small and hyperchromatic small round cells. The main characteristic pathologically is "Homer-Wright rosettes".

The embryonal tumors other than medulloblastoma have undergone substantial changes in their classification, with removal of the term primitive neuroectodermal tumor or PNET from the diagnostic lexicon. Much of the reclassification was driven by the recognition that many of these rare tumors display amplification of the C19MC region on chromosome 19 (19q13.42). If they have an amplification, they called embryonal tumors with multilayered rosettes C19MC-altered. In our case we could not identify the amplification, so it was called embryonal tumor with multilayered rosettes (NOS). The group of tumors, formerly known as PNETs, are Grade IV tumors. This means they are malignant (cancerous) and fast-growing. These are tumor types that belong to the following groups: 1) Medulloepithelioma, 2) CNS neuroblastoma, 3) CNS ganglioneuroblastoma and 4) Embryonal tumor with multilayered rosettes and other unspecified tumors. The common with these four subtypes of embryonal tumors is that they have not yet genetically been defined. Medulloblastoma, embryonal tumor with multilayered rosettes (C19MCaltered) and atypical teratoid/rhabdoid tumor (ATRT) have been genetically defined [8].

Conclusion

Primitive neuroectodermal tumors are highly malignant, originate from primitive neural tube or undifferentiated neuroepitelial cells. By using CT and MRI scans with contrast agents, the prominent enhancement reflects to an increased vascularity. Primarily occurs young children but there are about a 100 of cases with adults diagnosed with PNET. The appearance of a PNET in the ventricular system is rare and, in the literature, there are less than 5 cases like ours. The survival rate of this tumour type is less than 35% and additional studies are needed in predicting a more effective response rate.

References

[1] Norager, N.H., et al., *Reference values for intracranial pressure and lumbar cerebrospinal fluid pressure: a systematic review.* Fluids Barriers CNS, 2021. **18**(1): p. 19 DOI: 10.1186/s12987-021-00253-4.

[2] Dickinson, C.J., *Reappraisal of the Cushing reflex: the most powerful neural blood pressure*

stabilizing system. Clin Sci (Lond), 1990. **79**(6): p. 543-50 DOI: 10.1042/cs0790543.
[3] Sacco, T.L. and J.G. Davis, *Management of Intracranial Pressure Part II: Nonpharmacologic Interventions.* Dimens Crit Care Nurs, 2019. **38**(2): p. 61-69 DOI: 10.1097/DCC.0000000000000341.
[4] Hebel, R., M. Dubaniewicz-Wybieralska, and A. Dubaniewicz, *Overview of neurosarcoidosis: recent advances.* J Neurol, 2015. **262**(2): p. 258-67 DOI: 10.1007/s00415-014-7482-9.
[5] Ostrom, Q.T., et al., *CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016.* Neuro Oncol, 2019. **21**(Suppl 5): p. v1-v100 DOI: 10.1093/neuonc/noz150.
[6] He, X., et al., *A primitive neuroectodermal tumor in an adult: Case report of a unique location and MRI characteristics.* Medicine (Baltimore), 2018. **97**(7): p. e9933 DOI: 10.1097/MD.0000000000009933.
[7] Asmoniene, V., et al., *A primary primitive neuroectodermal tumor of the central nervous system in a 51-year-old woman: a case report and literature review.* Medicina (Kaunas), 2011. **47**(8): p. 440-5.
[8] Louis, D.N., et al., *The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary.* Acta Neuropathol, 2016. **131**(6): p. 803-20 DOI: 10.1007/s00401-016-1545-1.
[9] Kim, D.G., et al., *Supratentorial primitive neuroectodermal tumors in adults.* J Neurooncol, 2002. **60**(1): p. 43-52 DOI: 10.1023/a:1020207902659.
[10] Papadopoulos, E.K., et al., *A supratentorial primitive neuroectodermal tumor presenting with intracranial hemorrhage in a 42-year-old man: a case report and review of the literature.* J Med Case Rep, 2013. **7**: p. 86 DOI: 10.1186/1752-1947-7-86.
[11] Takeuchi, H., et al., *Cerebral primitive neuroectodermal tumour in an elderly patient with long-term survival.* J Clin Neurosci, 1998. **5**(4): p. 466-9 DOI: 10.1016/s0967-5868(98)90293-4.
[12] Pickuth, D. and U. Leutloff, *Computed tomography and magnetic resonance imaging findings in primitive neuroectodermal tumours in adults.* Br J Radiol, 1996. **69**(817): p. 1-5 DOI: 10.1259/0007-1285-69-817-1.
[13] Kampman, W.A., et al., *Primitive neuroectodermal tumours (PNETs) located in the spinal canal; the relevance of classification as central or peripheral PNET : case report of a primary spinal PNET occurrence with a critical literature review.* J Neurooncol, 2006. **77**(1): p. 65-72 DOI: 10.1007/s11060-005-9006-z.