

Primitive Neuroectodermal Tumor Presenting with Diffuse Leptomeningeal Involvement in a 55-Year-Old Woman: A Case Report and Brief Summary of Current Diagnostic Tests and Treatment

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Key Words

Primitive neuroectodermal tumor · Leptomeningeal involvement · Adult primitive neuroectodermal tumor

Abstract

Primitive neuroectodermal tumors (PNETs) are typically present as masses in children and adolescents, but rarely in adults. Diagnoses, management strategies, and prognostication factors are not well established in adult cases of PNETs. We describe the case of a central nervous system PNET diagnosed in a 55-year-old woman presenting with a sudden onset of symptoms consisting of increased intracranial pressure and findings of diffuse leptomeningeal enhancement and a small medullary lesion seen on MRI. Amongst the small database of PNETs diagnosed in adults, our case report stands out as one of few cases describing a primarily leptomeningeal PNET diagnosed on biopsy. We also review the literature on PNETs presenting with diffuse leptomeningeal disease and the treatment of PNETs in the adult population.

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Introduction

Primitive neuroectodermal tumors (PNETs) were first described in the literature by Hart and Earle in 1973. They are now classified by the World Health Organization as embryonal tumors comprising of undifferentiated or poorly differentiated neuroepithelial cells which appear to or which have the capacity to differentiate into astrocytic, neuronal, ependymal, muscular, or melanocytic lines [1]. PNETs involving the central nervous system can be classified as supratentorial tumors (including pineoblastomas) and infratentorial tumors, otherwise regarded as medulloblastomas [2, 3]. Central nervous system PNETs are typically found in children or adolescents and very rarely in adults, with less than 100 cases reported in the literature to date [4, 5]. This case details the diagnosis of a PNET involving the leptomeninges in the entire neural axis in a 55-year-old woman who presented with acute-onset cranial nerve abnormalities and findings of increased intracranial pressure. Multiple investigations were initially noncontributory, leading to a significant diagnostic delay. We review the literature regarding PNETs presenting with diffuse leptomeningeal involvement. We also summarize currently known diagnostic tests and management options for adult PNETs.

Case Presentation

A 55-year-old, previously highly functioning woman presented with a 1-week history of bitemporal, pressure-like, relapsing-remitting headache, nausea and vomiting, intermittent vertical diplopia, altered mental status, decreased cognition, and photophobia. The headaches were severe enough to wake her up from her sleep. She had no fevers or neck stiffness. She had a past medical history of osteoarthritis of the hip, managed with Celebrex, and was diagnosed with sinusitis 1 week prior to presentation. One year prior to this presentation, she had complained of headaches and visual disturbances, best described as scintillations, and suspected to have migraines with visual auras. She had no significant travel history and denied any alcohol, cigarette, or recreational drug use.

On the first day of admission to hospital, she was found to be alert and oriented with decreased attention and some word-finding difficulty. She was able to read but had difficulty writing complete sentences. She was noted to have incomplete abduction of the right eye and left-eye correcting nystagmus. Bilateral papilledema was noted on exam. There were no other cranial nerve abnormalities. She had normal strength, sensation, and reflexes in all of her extremities.

An initial CT scan of the head was unremarkable. Cerebrospinal fluid (CSF) analysis showed an elevated protein count of 4.58 g/l, a red blood cell count of $44 \times 10^6/l$ and a white blood cell count of $14 \times 10^6/l$, with an opening pressure greater than 27 mm H₂O. An MRI of the head and spine demonstrated an abnormal CSF signal in the FLAIR sequence as well as diffuse, smooth leptomeningeal enhancement over the basal meninges, extending into the sylvian regions bilaterally (fig. 1), and over the spinal cord and cauda equina (fig. 2). In addition, a nonenhancing focal intra-axial lesion of high T2/FLAIR signal intensity was identified on consecutive MRI scans in the left posteroinferior aspect of the medulla and cervicomedullary junction (fig. 3). Multiple CSF analyses over the subsequent few weeks after admission revealed continually elevated protein (maximum at 11 g/l) and high opening pressures on lumbar puncture (as high as 37 mm H₂O). An infectious workup of CSF samples was negative (including testing for syphilis, Lyme disease, HIV, toxoplasmosis, and microbial cultures). A gallium scan, chest X-ray, and CT scan of the thorax were negative for sarcoido-

sis. A thorough malignancy workup with pan scan of the head, chest, abdomen, and pelvis was negative.

A trial of steroids was initiated with 10 mg i.v. dexamethasone followed by 2 mg four times a day. As the patient continued to have an altered mental status, with worsening nausea and vomiting, a lumbar drain was placed, resulting in clinical improvement. Removal of the lumbar drain for more than 12 h led to a return of severe symptoms of intracranial pressure.

After several weeks of inconclusive investigations, a leptomeningeal biopsy from the area of enhancement in the basal meninges was attempted. The biopsy result did not reveal any malignant process. A ventriculoperitoneal shunt was placed as the patient continued to have elevated protein and intracranial pressure. Several weeks later, another biopsy of the leptomeninges in the posterior fossa and cerebellar tonsil was performed. The histology of the posterior fossa arachnoid tissue showed an undifferentiated tumor with a high nuclear to cytoplasmic ratio, numerous mitoses, scanty eosinophilic cytoplasm and no obvious differentiating cytoplasmic features or structures. The immunohistochemical studies showed very strong astrocytic differentiation and strong cytoplasmic synaptophysin positivity, along with a strong vimentin and a mild CD99 positivity. A few cells were positive for neurofilament (200 kDa). The nuclear proliferation index (Ki67) was up to 20–25%. The conclusion was undifferentiated neuroectodermal tumor, WHO grade IV, with divergent astrocytic and neuronal differentiation.

Radiotherapy was initiated. She received 1,600 cGy in 8 fractions over a course of 11 days, followed by another 4,000 cGy in 20 fractions to the brain and spinal cord over a 4-week period. Given the diffuse infra- and supratentorial leptomeningeal involvement and the presence of the medullary lesion, surgery was never attempted. A repeat MRI of the brain indicated interval worsening of the leptomeningeal enhancement in the basal region between the first and second radiation treatments, but she went through the second round of radiation as her clinical status had improved. Approximately 1 week after her last radiation therapy, she died due to sepsis secondary to radiation-induced pancytopenia.

Discussion

PNETs are classically considered to be tumors of childhood and adolescence; however, up to 100 adult presentations have been reported in the literature [1]. It has been found that only 0.7% of all malignant tumors in adults could be classified as PNETs, in contrast to PNETs in childhood comprising 15–25% of all primary central nervous system tumors [6, 7]. This case posed an interesting diagnostic dilemma as there are very few reported PNET cases presenting as a diffuse leptomeningeal process in the absence of a large solid tumor, though there was a focal area of intra-axial cervicomedullary abnormality, suspected to be a tumor. A literature search showed a total of 4 cases, both pediatric and adult, in whom the PNET presented in a similar manner. One case study described an 8-year-old boy presenting with signs of increased intracranial pressure, diagnosed with leptomeningeal PNET in the absence of an identifiable mass, who was treated with craniospinal irradiation and chemotherapy (with vincristine, carboplatin, cyclophosphamide, and lomustine) but eventually died due to the PNET 3.5 years from diagnosis [8, 9]. Szpak et al. [10] presented another case of leptomeningeal PNET in the absence of a solid tumor, diagnosed, on autopsy, in a 19-year-old woman who presented with meningismus, increased intracranial pressure and secondary hydrocephalus, and who died 18 months after initial presentation. Early diffuse leptomeningeal PNETs were also discussed by Ebinger et al. [11] who presented two

case reports of children aged 7 months and 5 years. The 7-month-old patient did not have a clear mass but did have basal cistern enhancement, similar to the patient discussed in our case report. The second patient reported by Ebinger et al. [11] presented with daily headaches associated with vomiting and papilledema. He had an unremarkable MRI initially but was found on repeat MRI 6 months later to have a large mass, biopsy-proven to be a PNET, and leptomeningeal enhancement around the tentorium. They proposed that perhaps leptomeningeal enhancement in PNET is an early manifestation of the disease, and that long-term identification of a tumor is possible on repeat scans, if the life expectancy of the patient allowed for it. In our case study, the finding of an ill-defined T2/FLAIR hyperintensity in the posterolateral medulla and cervicomedullary junction was questioned to be a possible primary site of PNET, though an autopsy was not performed to confirm this suspicion. Unfortunately, differentiating central and peripheral PNETs is unreliable simply based on location as both can occur either intracranially or extracranially along the neuroaxis. As a result, the current diagnosis of PNET is dependent on immunohistochemical diagnosis. Treatment strategies discussed in the literature tend to be reported on the basis of this histological classification, thereby making it useful to categorize these tumors in the clinical setting. Though genetic characterization in recent years has shown differences in PNET classes, only a few commercial options for diagnosis are available in most countries. The transmembrane glycoprotein product CD99 is typically found to be elevated in peripheral PNET, normal ependymal cells, leukocytes, some central nervous system neoplasms, and hematolymphoid neoplasms. In a retrospective study of 58 cases (43 diagnosed with PNET and 15 non-PNET cases), the use of the CD99 assay demonstrated 91% sensitivity and 80% specificity for a diagnosis of peripheral PNET [12]. The authors also found 100% specificity and 50% sensitivity for a diagnosis of PNET in the same patient population with the utilization of the FISH assay analyzing translocation at t(11;22), which is associated with 85% of peripheral PNETs as per the World Health Organization [1].

In this case report, as is typical of PNETs involving the central nervous system, the immunohistochemical studies showed poorly differentiated, densely packed cells with a high nuclear-cytoplasmic ratio and pleomorphic nuclei [4, 5]. Homer-wright rosettes were not seen in this case; however, these are not known to be essential for a definitive diagnosis [5]. Synaptophysin is expressed in cells exhibiting neuronal differentiation, and glial fibrillary acidic protein is highly expressed in cells with astrocytic differentiation – in this case report, this is congruous with the findings of cellular differentiation with astrocytic predominance on light microscopy [5]. The CD99 assay positivity was mild and not strong relative to the other biochemical markers, in keeping with a diagnosis of central nervous system PNET in this patient. In the biopsy originating from the posterior fossa, the diagnosis of medulloblastoma was entertained but excluded on the basis of the diagnostic imaging findings, the negative biopsy of one cerebellar tonsil and the predominant astrocytic differentiation of the tumor, a feature exceedingly rare in medulloblastoma. FISH analysis was not performed due to a lack of availability at this particular health center.

Due to the low incidence of PNETs in the adult population, there are no evidence-based guidelines for treatment recommended at present [5]. In the pediatric medulloblastoma population, the standard therapy is total resection of tumors, adjuvant chemotherapy and radiotherapy in order to achieve a higher prognostic benefit [3]. However, chemotherapy has not been effectively studied in the pediatric population with supratentorial PNETs. In adults, the effect of chemotherapy has not been reliably studied, thereby leading to the standard therapy being surgical resection and full-dose radiotherapy to the entire neuroaxis in PNET as there is typically a high penetrance of the CSF [6]. Several studies over the last few decades have shown a dose-dependent benefit of radiotherapy leading to long-term

disease-free survival, with various studies using anywhere between 15- and 25-Gy dosages to higher dosages of 55 Gy [13, 14]. The patient in our case received two cycles of radiotherapy as described above, the doses of which certainly fall within these ranges.

In adults, most available data stem from retrospective studies. A long-term follow-up study and review of chemotherapy (with diethylcarbamazine) in adults indicated no significant difference in progression-free survival and overall survival between high-risk patients treated with chemotherapy and radiotherapy versus low-risk patients treated with radiotherapy alone [2, 3]. Apart from the fact that some of these studies had inclusion criteria wherein patients over the age of 15 were categorized as adults, there are no reliable trials to date in adults with PNETs comparing both treatment groups with chemotherapy alone versus chemotherapy and radiotherapy versus radiotherapy alone.

Conclusion

This case describes a 55-year-old woman presenting with diffuse leptomeningeal enhancement diagnosed as being secondary to PNET. This is one of very few reported cases of PNET presenting with diffuse leptomeningeal enhancement in the absence of a large, solid, localized tumor. Her clinical course and treatment are discussed here, along with a brief summary of the diagnosis, and thus far studied treatment strategies in adult PNET cases.

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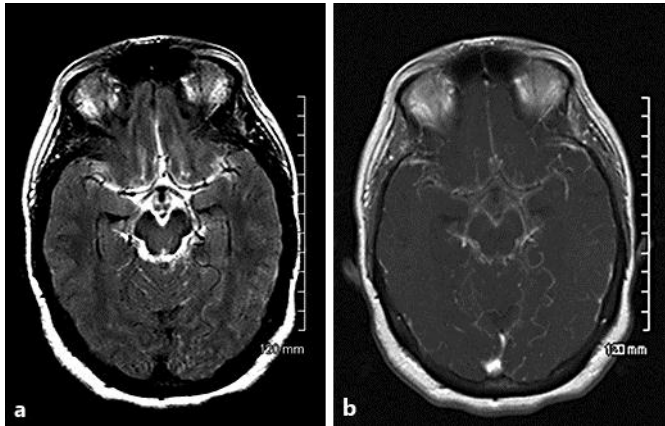


Fig. 1. **a** Axial FLAIR image shows increased signal intensity of the subarachnoid spaces at the level of the basal cisterns. **b** Postcontrast axial T1-weighted sequence shows the corresponding leptomeningeal enhancement in the basal cisterns.



Fig. 2. Sagittal T1-weighted sequences of the spine after gadolinium injection demonstrate diffuse leptomeningeal enhancement along the brainstem, and along the spinal cord and proximal cauda equina nerve roots.

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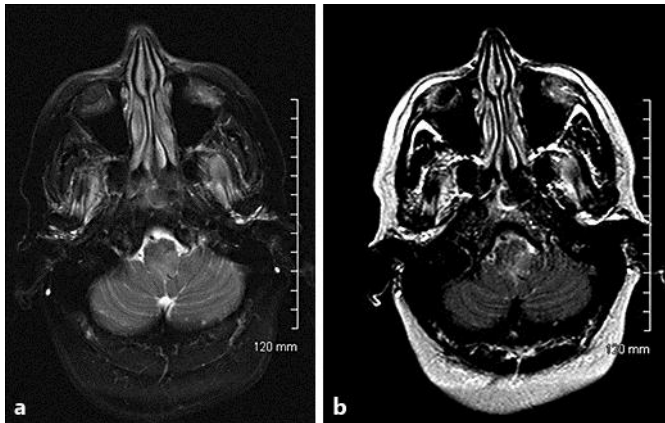


Fig. 3. Axial T2-weighted (a) and axial FLAIR (b) images demonstrate an ill-defined expansile intra-axial lesion in the left posterolateral aspect of the medulla. Note the increased CSF signal intensity within the premedullary cistern.