

MULTIPLE SYSTEMIC METASTASES OF POSTERIOR FOSSA - PRIMITIVE NEUROECTODERMAL TUMOR (PF-PNET) IN ADULT

Case report

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ABSTRACT - We present the case of a 30-year female patient with multiple systemic metastases of posterior fossa primitive neuroectodermal tumor (PF-PNET) and present a review concerning the usual presentation, sign and symptoms, radiological aspects, pathways of spread, genetic patterns and treatment of PF-PNET. The biological behavior of PF-PNET is analyzed taking into consideration the presence of systemic metastases.

KEY WORDS: medulloblastoma, metastases, primitive neuroectodermal tumor (PNET).

Metastases sistêmicas múltiplas de tumor neuroectodérmico primitivo (PNET) na fossa posterior em adulto: relato de caso

RESUMO - A presença de metástases múltiplas sistêmicas decorrentes de um tumor neuroectodérmico primitivo (PNET) numa paciente de 30 anos é relatada. É feita pelos autores revisão desta patologia, incluindo sua apresentação clínica, sinais e sintomas, aspectos radiológicos, vias de disseminação, aspectos genéticos e tratamento. É abordado na discussão do caso particularmente o comportamento metastático dos meduloblastomas, comparativamente com os não metastatizantes.

PALAVRAS-CHAVE: meduloblastoma, metástase, tumor neuroectodérmico primitivo (PNET).

The term medulloblastoma was coined by Bailey and Cushing in 1925¹ after the observation of malignant midline tumors of posterior fossa with unique features. Hart and Earle in 1973² used the term primitive neuroectodermal tumor (PNET) during the description of supratentorial tumors with small, round and blue cells. Rorke in 1983³ described that these cells observed in supratentorial tumors were undistinguishable from those observed in medulloblastomas. The World Health Organization, after that, formally introduced the term posterior fossa - primitive neuroectodermal tumor (PF-PNET) for Medulloblastomas. In 1936, Nelson⁴ reported the first case of metastases of medulloblastoma outside the Central Nervous System (CNS). Thereafter, some reports of spread outside of the CNS of PF-PNET have been published, and most of them in pediatric population. PF-PNET represents about 15 to 30 % of

childhood brain tumors⁵⁻⁸. The frequency in the adult population ranges from 1% to 2% among CNS tumors⁶⁻⁸. Metastases outside the CNS are rare. The overall incidence of non-CNS involvement by PF-PNET comprises approximately 7%⁸⁻⁹.

We present a case of multiple systemic metastases of a PF-PNET in a female adult patient, and a literature review.

CASE

A 30-year female patient presented as an outpatient to the University Hospital complaining of generalized bone pain. Her physical examination upon arrival was unremarkable and laboratory evaluation showed mild anemia, elevation of sedimentation rate and hypercalcemia. She had a medical history of resection of a medulloblastoma performed four years before. One year after the first surgical approach, local recurrence occurred and another gross to-

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Received 3 June 2002, received in final form 29 August 2002. Accepted 12 September 2002.

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Fig 1. Absence of intracranial recurrence of the medulloblastoma in a postoperative axial CT scan with contrast enhancement.



Fig 2. Sagittal T2-weighted MRI of the spinal cord showing an extensive intra-axial metastasis. (A = anterior).

tal resection of the cerebellar tumor was done, followed by posterior fossa radiotherapy performed with 56 Gy and craniospinal axis radiotherapy with 36 Gy.

She continued to be followed in the outpatient clinic and two months later she presented at emergency room with poor general status, dyspnea, lumbar pain and progressive paraparesis with sphincter disturbance, and pyramidal signs in both lower extremities. Her clinical examination also revealed a hard nodule at eleventh left rib. It was not possible to define then a spinal cord level of sensitive deficit. X-Ray evaluation showed extensive bilateral pleural effusion and blastic lesions at ribs and vertebral bodies. The suspicion of bone metastases was enhanced by osseous radionuclide study. Thoracentesis fluid analysis was positive for malignant cells. Brain imaging did not show local posterior fossa or supratentorial recurrence (Fig 1). The spinal cord Magnetic Resonance (MR) study showed multiple lesions compressing the spinal cord from T3 to T11, lesions at paravertebral musculature, pleural and lung nodules (Figs 2 and 3). She was submitted to additional spinal axis radiation therapy (0,8 Gy) but a complete sensitive, motor and sphincter deficit developed in spite of the treatment. A bone excision biopsy was performed confirming undifferentiated small malignant cells with tumor markers compatible with medulloblastoma (Sinaptofisín +, GFAP +, Vimentin +, S100 -, LCA -, AE1AE3 -, Neurofilaments -). Due to her bad clinical status, chemotherapeutic regimen was not performed and the patient died two months later.

DISCUSSION

PF - PNET is a rare tumor in adult patients and systemic metastases are even rarer. The PF - PNET has a male preponderance 2:1^{6,10} and the average age of presentation is between 24 - 34 years when the tumor occurs in adults^{6,8,9}. Headache is the most common symptom, followed by ataxia⁶. Papiledema, nausea, vomiting, cranial nerve palsies, blurred vision and mental changes are also found. When extra cranial metastases are present, hypercalcemia, thoracic or abdominal pain, dyspnea and bone nodule are the most prominent features.

Bone is a frequent site for PF - PNET systemic metastases¹¹⁻¹³ and blastic lesions are the most frequent radiological pattern¹⁴. Lymph nodes, lungs, abdominal cavity, breast and pancreas are also sites of PF - PNET spread outside the CNS^{15,16}. Different pathways of spread of PF - PNET cells have been postulated since different organs have been described as harboring metastases. The possible routes for dissemination are lymphatic vessels, cerebrospinal fluid in the sites where nerve fibers leave the CNS, and blood, through arachnoid villi and the increased blood brain permeability^{9,10,17}.



Fig 3. Axial T1-weighted image showing a large right pulmonary (thick arrow), vertebral body (arrow head), left rib (curved arrow), and intra-axial metastases (dotted-line arrow). (R = right).

Surgery has been cited as a pathway for dissemination since the lumen of blood vessels is exposed and tumor cells may be carried to distant sites. Ventricle Peritoneal shunt (VP-shunt) is described as another pathway for dissemination of tumor cells. These observations are based on numerous publications reporting the greater incidence of metastases in patients who undergo surgery^{10,17} or VP-shunt⁹. However, several reports considered the dissemination through surgery or VP-shunt questionable, since regardless of whether the surgical procedure was performed, the location of extraneural metastases, incidence and the time of appearance of systemic disease are the same. This suggests that both the surgery and insertion of VP-shunt do not increase the likelihood of an unfavorable prognosis due to systemic metastases⁷. Complete tumor resection decreases the frequency of local recurrence, however a relationship between the extent of surgical resection and extraneural metastases has not been found^{5,7}.

The gene expression of the PF - PNET that metastasizes is probably different from the gene expression of the PF - PNET that is restricted to the cerebellum. This is a possible explanation of the presence of systemic metastases in some patients, irrespective of the treatment applied, age of the patient, extent of tumor resection, sex and the presence of VP shunt⁷. Platelet - derived growth factor receptor alpha (PDGFRA) and members of the downstream RAS / mitogen - activated protein kinase (MAPK) signal

transduction pathway are up regulated in metastatic PF - PNET, and may act as therapeutic target along with HAS proteins and PDGFRA inhibitors¹⁸. The presence of the iso (17q) chromosome has also been reported as prognostic factor¹⁹.

The treatment of the PF - PNET requires surgical resection as complete as possible and the rational use of radiation and chemotherapeutic drugs as an adjuvant therapy. There are many regimens for radiation therapy (XRT). Posterior fossa doses are defined around 55 Gy and craniospinal axis doses around 30 Gy (20) and 35 Gy²¹⁻²³. Radiation therapy is recommended for all patients after surgical procedure as prophylactic treatment to prevent local and distant CNS recurrence.

The benefits of chemotherapy are yet to be straightforwardly defined, as compared to radiation therapy. Studies addressed to evaluate chemotherapy have used different classifications for low and high risk patients and the groups of patients have not been uniform. However, there is a tendency towards the use of a combination of Vincristine, CCNU, prednisone, procarbazine and methotrexate^{16,21,22,24} for rescue therapy or for high risk patients. This includes those with distant metastases, bone marrow tumoral cells, spinal seeding and VP shunt. Unfortunately, intensive chemotherapeutic regimens fail to show positive effects and eventually replace or diminish XRT^{16,21,22} in order to lower its side effects especially in children.

The chance of cure for PF – PNET has improved in the last decades^{16,25}. A five year survival has increased from previous reports of approximately 50%⁵ to recent reports showing a higher range (50 to 80%) for a bigger time span (ten years)^{16,23}. The reasons for the increase in survival rates are due to more complete surgical resection achieved with microoperative techniques, along with the rational use of chemotherapy and radiation therapy.

Systemic metastases constitute a rare complication of PF - PNET, that changes the outcome and are an obstacle to long term survival. Prevention to local and CNS recurrence is possible and usually performed. The presence of distant metastases, however, is difficult to avoid with our current therapy^{8,16}. Further studies on molecular biology and the gene expression of the PF - PNET may shed light on the biological properties of the tumors that metastasize and the comprehension of the pathophysiology may guide new forms of treatment.

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