Clinical Aspects and Prognostic Factors of Neuroblastoma: Case Report

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Aspectos Clínicos e Fatores Prognósticos do Neuroblastoma: Relato de Caso

Aspectos Clínicos y Factores Pronósticos del Neuroblastoma: Reporte de Caso

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ABSTRACT

Introduction: Neuroblastoma is an extracranial tumor originated from neural crest cell failures. It's the most common malignant neoplasm among infants and it presents a very heterogeneous clinical profile. The objective of the article is to report the case of a patient with neuroblastoma in advanced stage and satisfactory survival, despite the poor prognostic factors. **Case report:** Female patient, 1 year and 4 months old who presented irritability, abdominal distention and intermittent fever with three months of evolution. In physical exam, she presented alopecia suggestive of trichotillomania, cervical, inguinal and axillary lymph node enlargement and abdominal distention. Abdominal computed tomography evidenced expansive mass, measuring 6.8 x 5.8 x 4.0 cm, located in the left anterior pararenal space. Bone scintigraphy and nuclear magnetic resonance showed images suggestive of distant secondary implants. After total tumor excision, it was confirmed poorly differentiated neuroblastoma, with non-amplified *MYCN* gene and unfavorable histology. Bilateral iliac crest biopsy revealed bone marrow areas occupied by the neoplasm, suggesting bone marrow infiltration. As this was a stage IV neuroblastoma, multimodal therapy was established with adjuvant chemotherapy after surgery, followed by autologous bone marrow transplantation, radiotherapy at the primary site of the lesion and at the sites of bone metastases and use of 13-cis-retinoic acid. **Conclusion:** Despite presenting several indicators of poor prognosis (age, stage IV, bone metastases, bone marrow infiltration), the patient has been in complete remission of the disease for 39 months.

Key words: neuroblastoma; prognosis; medical neoplasms; case reports.

RESUMO

Introdução: O neuroblastoma é um tumor extracraniano originado de falhas das células da crista neural. É a neoplasia maligna mais comum dos lactentes e apresenta perfil clínico bastante heterogêneo. O objetivo deste artigo é relatar o caso de um neuroblastoma em estádio avançado e sobrevida satisfatória, a despeito dos fatores prognósticos desfavoráveis. **Relato do caso**: Paciente feminina, 1 ano e 4 meses, iniciou quadro de irritabilidade, distensão abdominal e febre intermitente com três meses de evolução. Ao exame físico, apresentou alopecia sugestiva de tricotilomania, linfonodomegalia cervical, inguinal e axilar e distensão abdominal. A tomografia computadorizada de abdome evidenciou massa expansiva, medindo 6,8 x 5,8 x 4,0 cm, localizada no espaço pararrenal anterior esquerdo. À cintilografia óssea e ressonância nuclear magnética, foram visualizadas imagens sugestivas de implantes secundários a distância. Após exérese tumoral total, foi confirmado neuroblastoma pouco diferenciado, com gene *MYCN* não amplificado e histologia desfavorável. Biópsia da crista ilíaca bilateral revelou áreas compatíveis com infiltração medular. Por se tratar de neuroblastoma estádio IV, estabeleceu-se terapêutica multimodal, com quimioterapia adjuvante após cirurgia, seguida de transplante autólogo de medula óssea, radioterapia no sítio primário da lesão e nos locais de metástases ósseas e uso de ácido 13-cis-retinoico. **Conclusão**: Apesar de apresentar diversos indicadores de mau prognóstico (idade, metástases ósseas, estadiamento IV, infiltração medular), a paciente permanece em remissão completa da doença há 39 meses.

Palavras-chave: neuroblastoma; prognóstico; neoplasias; relatos de casos.

RESUMEN

Introducción: El neuroblastoma es un tumor extracraneal originado a partir de fallas de células de cresta neural. Es la neoplasia maligna más común de los bebés y tiene un perfil clínico muy heterogéneo. El objetivo de este artículo es informar un caso de un paciente con neuroblastoma avanzado y supervivencia satisfactoria, a pesar de los factores de mal pronóstico. **Relato del caso:** Paciente femenina, de 1 año y 4 meses, comenzó con irritabilidad, distensión abdominal y fiebre intermitente con tres meses de evolución. En examen físico, presentó alopecia sugerente de tricotilomanía, ganglio linfático megaly en las cadenas cervicales, inguinales y axilares y distensión abdominal. La tomografía computarizada del abdomen mostró una masa expansiva, que mide 6,8 x 5,8 x 4,0 cm, situada en el espacio pararrenal anterior izquierdo. La centellografía ósea y la resonancia magnética, se visualizaron imágenes sugestivas de implantes secundarios a distancia. Después de la escisión total del tumor, se confirmó neuroblastoma poco diferenciado, con un gen *MYCN* no amplificado e histología desfavorable. La biopsia de la cresta ilíaca bilateral reveló áreas de la médula ocupadas por neoplasia compatibles con infiltración medular. Debido a que se trata de neuroblastoma en estadio IV, se estableció terapia multimodal, con quimioterapia adyuvante después de la cirugía, seguida de trasplante autólogo de médula ósea, radioterapia en el sitio primario de la lesión y en los sitios de metástasis óseas y uso de ácido 13-cis-retinoico. **Conclusión:** A pesar de presentar varios indicadores de mal pronóstico (edad, metástasis óseas, estadio IV, infiltración medular), el paciente ha permanecido en remisión completa de la enfermedad durante casi 39 meses.

Palabras clave: neuroblastoma; pronóstico; neoplasias; informes de casos.

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INTRODUCTION

Neuroblastoma is a malignant neoplasm derived from the defects of migration, maturation or differentiation of the neural crest cells[1]. The primary sites are adrenal bone marrow (60%), retroperitoneum (20%), mediastinum (10%), pelvis (6%) and neck (2%)[2].

It is the most common extracranial tumor in infants with frequent diagnosis at the first year of life and median age of 18 months[3]. One of its features is the heterogeneity with spontaneous regression in some patients and metastasis and poor prognosis in others[1].

The objective of the present study is to report a case of neuroblastoma with satisfactory survival, despite poor prognosis. It is a quite uncommon pathology and unspecified clinic presentation which can make the diagnosis and early management difficult and reduce successful therapeutic. Healthcare professionals should establish differential diagnosis and present a secondary positive outcome to the treatment prescribed, possibly contributing to the scientific literature.

The Informed Consent Form (ICF) was signed by the patient's legal representative who agreed to participate voluntarily. The Institutional Review Board (IRB) of "*Universidade Federal de Ouro Preto*" approved the study, report number 4.668.888, CAAE (Submission for Ethical Review) 44375221.4.0000.5150, in compliance with ethical and scientific rules of Resolution 466/2012[4] of the National Health Council.

CASE REPORT

Female patient, 1 years and 4 months old, healthy, admitted to a tertiary hospital with irritability, abdominal distension and intermittent fever with three months of evolution. The infant was irritated at the physical exam; she presented alopecia suggestive of trichotillomania, cervical, inguinal and axillary lymph node enlargement and abdominal distension.

Lab tests revealed progressive normocytic/normochromic anemia, leukocytosis with left deviation and increase of acute phase inflammatory proteins. Thorax radiography and computed tomography (CT) did not show alterations and echocardiogram revealed mild pericardial effusion with normal biventricular function. Neck CT displayed bilateral cervical lymph node enlargement, probably reactional, and total abdominal CT showed expansive, circumscribed mass, measuring 6.8 x 5.8 x 4.0 cm, with amorphous calcifications and central areas of necrosis at the left anterior pararenal space, without cleavage plane with the left adrenal gland (Figure 1).

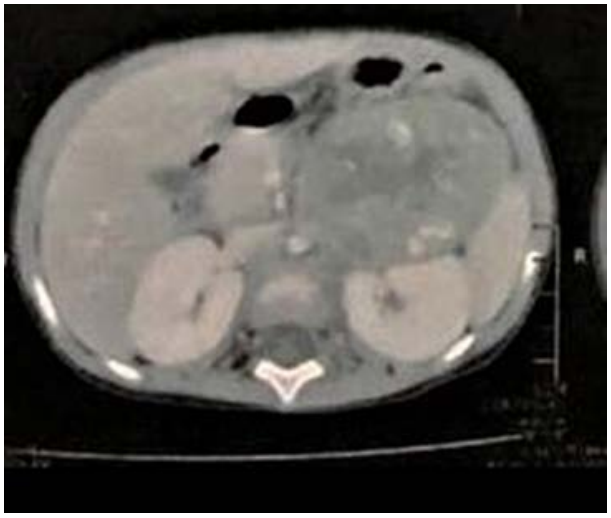

Figure 1. Abdominal computed tomography. Expansive mass at the left anterior pararenal space

A diagnosis of neuroblastoma was suggested; bone scintigraphy and nuclear magnetic resonance (NMR) revealed images suggestive of secondary implants in L1, L2, L4, femur and iliac crests. Fifteen days after admission, exeresis and bilateral iliac crest biopsy (Figure 2) were performed. The pathological report revealed neoplastic lesion characteristic of poorly differentiated neuroblastoma, with small anaplastic foci and intermediate mitotic/karyopyknotic index, metastasis to left peri-hilar lymph node and bone marrow areas occupied by the neoplasm compatible with bone marrow infiltration.

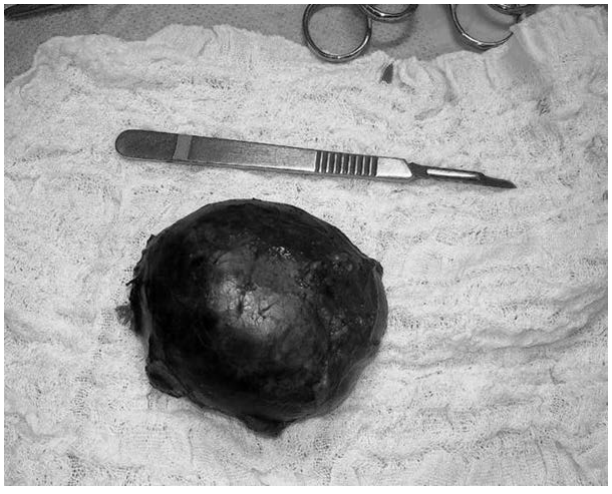

Figure 2. Tumor mass post exeresis

After diagnosis and staging – established as stage IV neuroblastoma according to the International Neuroblastoma Staging System (INSS)[5] – with non-amplified gene *MYCN* and unfavorable histology, the disease was classified as high risk by the attending team with chemotherapy initiated following the protocol

CCG 3891: cisplatin, doxorubicin, etoposide and cyclophosphamide. Five chemotherapy cycles were performed every other 21 days.

After the last cycle, the patient was submitted to autologous bone marrow transplantation with satisfactory recovery. Post-transplantation imaging exam did not display bone lesions. Radiotherapy was applied then at the primary site and bone metastases and later, 13-cis retinoic acid for six months.

The patient is in complete remission for 39 months without signs of neoplasm and age-appropriate psychomotor development and growth. Figure 3 portrays the timeline of the evolution of the case.

DISCUSSION

Neuroblastoma accounts for 10% of the cases of childhood cancer with prevalence of one at each seven thousand live births in Brazil[6].

The diagnosis of abdominal tumors, mainly at initial stages, is difficult due to unspecific symptoms – pain or abdominal fullness, palpable abdominal mass in asymptomatic children and intestinal obstruction[7,8].

In up to 35% of the children with apparent localized disease, lymph nodes are compromised. The hematogenic dissemination affects bones, bone marrow, skin and liver mostly. When metastatic dissemination to bones and bone marrow occurs, pain, mainly in ambulation are noticed in addition to alteration of the blood count and fever. In children unable to express their complaint, bone pain can manifest as an inexplicable irritability[7].

After comparing with the literature, the clinical condition is an infant younger than 5-years old with abdominal distension, intermittent fever and irritability and unspecified lab alterations.

The American Society of Clinical Oncology determines that the definitive diagnosis of neuroblastoma needs unquestionable histological confirmation or evidence of bone marrow metastasis with concomitant elevation of catecholamines in the urine[7].

CT of the whole abdomen revealed expansive mass. The histological analysis confirmed the diagnosis and investigation of metastasis followed. The INSS acknowledges the results of the physical exam, imaging (CT, NMR and scintigraphy with metaidobenzylguanidine – MIBG) and biopsy of the tumor and other tissues to determine the staging[9]. The conclusion after thorough propaedeutics is IV stage neuroblastoma defined as a disseminated tumor to other parts of the body as remote lymph nodes, bones, liver, skin, bone marrow or other organs but the child does not meet the criteria for stage IV S.

As the neuroblastoma has great clinical heterogeneity, the Children's Oncology Group (COG)[10] stratifies the patient at low, intermediate or high risk to determine the prognosis based in the following factors: age at diagnosis, stage to define extent of the disease by INSS (replaced by the International Neuroblastoma Risk Group – INRG), tumor histology utilizing the International Neuroblastoma Pathology Classification (INPC) criteria, *MYCN* oncogene status and tumor cell ploidy.

The case was classified as high risk according to INSS, but with the new system, was revised to intermediate risk based on the patient age (high risk for those older than 18 months of age). The revision was developed to establish a consensus approach for pretreatment risk stratification to allow the comparison among clinical trials conducted by different cooperative groups[10].

Tumor histology can be classified as favorable or unfavorable, as less differentiated, worst is the

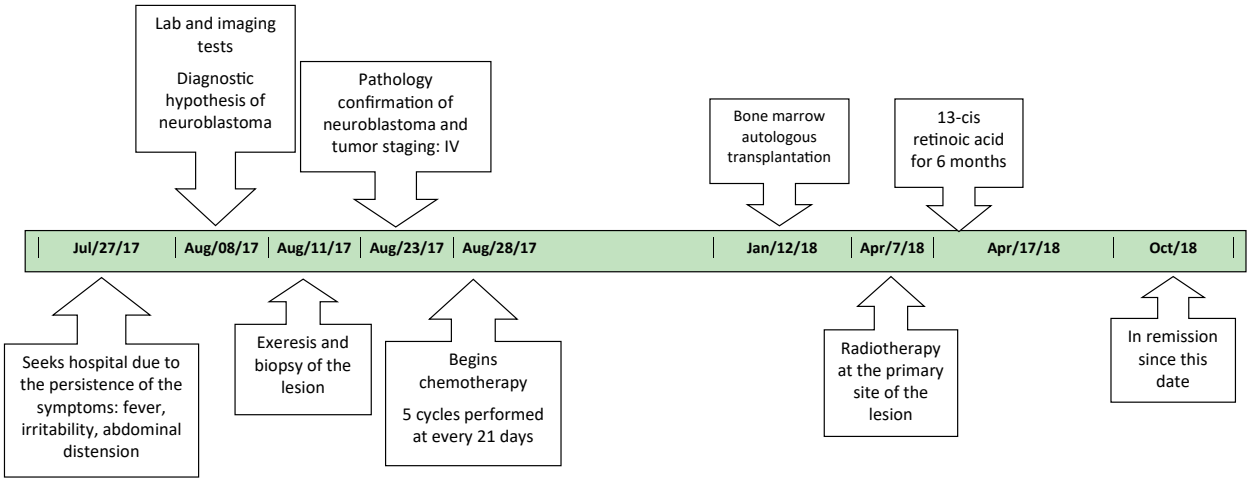

Figure 3. Timeline

prognosis. Chromosomal characteristics are important as amplification of oncogene *MYCN*, at least with ten copies and associated with rapidly progressive disease[11]. According to the chart, the histology was unfavorable, but a non-amplified *MYCN* oncogene can be considered a single factor for favorable prognosis.

Despite innumerous factors described by the literature to determine the prognosis of neuroblastoma, only two are independent and fully proven: age and staging by INSS. Neuroblastoma can be classified in three prognostic groups[12]:

1. Patients in stages I, II and IV S: require surgery or low-dosage adjuvant chemotherapy – 85% survival.
2. Patients in stages III and infants stage IV: require conventional chemotherapy and primary tumor resection – 60% survival.
3. Patients older than one-year of age in stage IV: require multimodal treatment (intensive chemotherapy, surgery, bone marrow transplantation, retinoic acid etc.) – 15% to 25% survival (30% to 40% with retinoic).

The case was classified as stage IV according to INSS, with worst prognosis for this classification.

Typically, the treatment of neuroblastoma (modality, intensity and duration) is defined according to COG's[10] stratification of risk followed by protocol CCG 3891. It is a prospective study which evaluated whether the association of myeloablative chemotherapy, irradiation and autologous bone marrow transplantation would improve survival in comparison with follow-up myeloablative chemotherapy in children with high-risk neuroblastoma.

A second randomization was carried out to evaluate whether the utilization of 13-cis retinoic acid would extend survival. In a study by Berthold F, Boos J, Burdach S, et al, the patients were treated with cisplatin, doxorubicin, etoposide and cyclophosphamide in five cycles with surgery and adjuvant radiotherapy. In addition, they were submitted to autologous bone marrow transplantation and 13-cis retinoic acid. The result was 3-year event-free survival (EFS) of 68%, an increase when compared to patients of the other prognostic group[13].

Comparing complete with partial resection of the primary tumor, there is no consensus about what is best for patient survival, but some authors concluded there are benefits of complete surgical resection. A retrospective study with 40 patients with stage IV neuroblastoma (INSS) and metastatic disease at diagnosis, 72% were submitted to radical surgery and 28% to partial resection or biopsy. Of the total, 43% had operative or postoperative complications. Those submitted to radical surgery had 5-year global survival (GS) and EFS significantly better (GS=66%; EFS=58%) compared with patients who underwent partial surgery (GS=12%; EFS=12%) evaluated by the Kaplan-Meier survival curve and log-rank test[14].

According to COG[10], monitoring of patients with neuroblastoma should be carried out after maintenance therapy to detect recurrence signs and help the family to deal with adverse events. A study conducted in China with 116 patients with neuroblastoma concluded that the mean time for recurrence was 19 months for patients who achieved full response after multidisciplinary treatment[15]. Another study carried out in São Paulo (Brazil) with 258 patients showed mean recurrence time of 18.2 months[5]. The current patient is in complete remission for 39 months without recurrence.

CONCLUSION

The confirmed diagnosis of neuroblastoma of the present case determined the treatment recommended by the literature. Notwithstanding many unfavorable prognostic factors, the patient evolved well, remains in complete remission for 39 months with age-appropriate growth and neuropsychomotor development.

CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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