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CLINICOPATHOLOGICAL CASE

Alveolar rhabdomyosarcoma: origin and prognostic implications of molecular findings

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Prognostic significance

Abstract We present the case of a 2-year-old male patient with a facial tumor partially treated with chemotherapy before his admission to our institution. The tumor involved from the frontal region to the maxillary floor, the orbit, and the maxillary and sphenoid sinuses. The histopathological diagnosis revealed a stage IV alveolar rhabdomyosarcoma with infiltration to bone marrow and cerebrospinal fluid. He was managed with four cycles of adriamycin, actinomycin, cyclophosphamide and vincristine; cisplatin and irinotecan were added to the last cycle. The tumor had a 50% size reduction, but the patient died after a neutropenia and fever episode.

The aggressive behavior of alveolar rhabdomyosarcoma has been associated with the expression of oncogenic fusion proteins resulting from chromosomal translocations, particularly t(2;13)(q35;q14) PAX3/FOXO1, and t(1;13)(p36;q14) PAX7/FOXO1 which were present in this patient.

PALABRAS CLAVE
Rabdomiosarcoma;
Rabdomiosarcoma alveolar;
Infancia;
Translocación;
Significación pronóstica

Rabdomiosarcoma alveolar: origen de los hallazgos moleculares e implicaciones pronósticas

Resumen Se presenta el caso de un niño de dos años de edad con un tumor facial tratado parcialmente con quimioterapia anterior a su admisión en este hospital. El tumor abarcaba desde la región frontal hasta el piso maxilar, la órbita y los senos esfenoidales y maxilares. El diagnóstico histopatológico reveló un rabdomiosarcoma alveolar estadio IV con infiltración a la médula ósea y fluido cerebroespinal. El paciente fue tratado con cuatro ciclos de adriamicina, actinomicina, ciclofosfamida y vincristina; al último ciclo se añadieron cisplatino e

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irinotecan. El tumor se redujo en 50% de su tamaño, pero el paciente murió tras un episodio febril y neutropénico. La agresividad del rabdomiosarcoma alveolar se ha asociado con la expresión de proteínas oncogénicas de fusión provenientes de translocaciones cromosomales, particularmente t(2;13) (q35;q14) PAX3/FOXO1 y t(1;13) (p36;q14) PAX7/FOXO1, presentes en este paciente.

1. Introduction

Rhabdomyosarcoma (RMS) is a malignant tumor of striated muscle of mesenchymal origin regarded as the most recurrent soft tissue sarcoma in children and adolescents, with an annual incidence of 4.3 cases per million. Approximately two-thirds of the cases are diagnosed in children (typically around 6 years of age), and are slightly more common in males, with a male/female ratio of 1.4:1.[1] Due to its origin in a totipotent cell, rhabdomyosarcomas not only occur in skeletal muscle but other locations, such as the head, neck, genitourinary tract and bile ducts. Approximately 40% of RMS occur in the region of the head and neck, 20% in the genitourinary region, 20% in the extremities and the remaining 20% in other sites.[1]

The embryonal and alveolar variants are the more frequent histological types, comprising 70 to 20% of the cases, respectively.[2] The embryonal rhabdomyosarcoma (ERMS) is the most common subtype in infants and young children and represents more than two-thirds of all the RMS.[1,3] This tumor is composed of a soft mixture of fusiform cells with areas of soft, loose stroma, and it is associated with loss of heterozygosity at the 11p15 locus.[3] The tumors that are located in the head, neck, and genitourinary region often present this histological type.

Alveolar rhabdomyosarcomas (ARMS) usually appear in adolescence; they are typically located in the extremities and have a high capacity to metastasize.[1,4] Their histology is characterized by a septum of fibrous connective tissue with neoplastic cells attached (Figure 1A), similar to the alveolar spaces observed in the lung, where some of the cells detach and occupy the space. It is composed of cells uniformly polygonal with high grade round or oval hyperchromatic nucleus (Figure 1B).[1] Unlike the ERMS, the ARMS exhibit two particular types of chromosomal translocations: between chromosomes 2 and 13, t (2;13) (q35;q14), and between chromosomes 1 and 13, t (1;13) (p36;q14), which occur in 80% of the cases.[4] These genetic alterations lead to the fusion of two families of transcription factors. The first is located on chromosome 1 or 2 and involves transcription factors PAX3 and PAX7, respectively. PAX family of transcription factors is a group of genes involved in the differentiation of organs and tissues, and possess an N-terminal DNA binding domain, which includes a paired box, homeobox motifs, and a C-terminal trans-activation domain, while the second class involves members of the family of the forkhead (FKHR) transcription factors or FOXO1.

The transcription factors of PAX and FOXO1 families possess an N-Terminal domain of union with the DNA and a C-terminal domain of transactivation. The breaking points for PAX and FOXO1 occur at introns 7 and 1, respectively. Fused genes codify for two chimeric proteins with oncogenic activity, PAX3/FOXO1, and PAX7/FOXO1. These proteins are composed of a 5′ domain of union to the DNA (PAX) and a 3′ transactivation domain (FOXO1).[4] It has been demonstrated that PAX3/FOXO1 and PAX7/FOXO1 transcripts are present in 55 and 22% of the ARMS, respectively, while the remaining ARMS are negative for the fusion gene.[5] It is known that ARMS with the PAX7/FOXO1 translocation have a much more favorable prognosis compared to those who carry the translocation PAX3/FOXO1. The median 4-year survival for the former is 75% and 8% for the latter.[6] The patients with ARMS who often have metastasis at diagnosis have a short median survival. In addition, the presence of proteins of the fusion gene PAX3/7-FOXO1 is associated with an unfavorable prognosis.[2]

2. Clinical case

A male patient of two years and three months of age, native of Yucatan, who had no significant past medical history until five months of age when a violet bulk appeared in his left nostril. According to the parents, he was treated with chemotherapy and radiotherapy in a local clinic, with remission of the tumor two months later. When the boy was two years old, the tumor appeared again, so they came to our hospital.

On physical examination, his weight was 10.4 kg and his height 100 cm. He was awake, his right eye had normal pupil light reflex, but the left eye was not assessable because of a tumor located in the middle of the face, predominantly on the left side, purplish, fetid, fixed to deep planes. Teeth were displaced. He had no lymphadenopathies in the neck. No abnormalities were found in the thorax, abdomen or limbs.

Computed tomography (CT) showed a lobed tumor, with well-defined borders which involved from the frontal region up to the maxillary floor. Histopathological diagnosis was stage IV alveolar rhabdomyosarcoma with infiltration to bone marrow and cerebrospinal fluid. He was managed with antibiotics and began chemotherapy with adriamycin, actinomycin, cyclophosphamide, and vincristine. The first cycle was completed, and he was discharged. He received four cycles of chemotherapy, with a tumor size reduction of 50%.