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New Type of Malignant Neoplasm in Childhood - Epithelioid Neoplasm with Fusion of EWSR1/CREM Genes: Case Report

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1. Abstract

We present a case of a 9-year-old child with a malignant epithelioid neoplasm located in the retroperitoneum that was found to have a fusion of the ESWR1/CREM genes, confirmed through anatomopathological examination, immunohistochemical, and molecular biology studies. While similar cases have been reported in the literature for adult patients, they are very rare in children and appear to represent a new type of tumor. Our case emphasizes the importance of the correlation between pathological anatomy and genetics.

2. Introduction

Recent advancements in molecular biology have greatly enhanced our under-standing of the genetic factors associated with pediatric cancer, thereby improving the diagnosis, classification, and treatment of this disease [1]. The newly published WHO 2020 classification for pediatric cancers represents a shift from the traditional histology-focused system to an integrated approach that incorporates molecular entities [2]. Many pediatric cancers are characterized by gene fusion events, which can aid in oncological diagnosis and prognosis [1, 3]. One example is the fusion of the EWSR1 gene with the CREB (cAMP response element-binding protein) gene, resulting in the EWSR1/CREB gene fusion. This gene fusion can induce rearrangements that promote carcinogenesis and potentiate the development of various tumors with mesenchymal, neuroectodermal, and epithelial characteristics, ranging from benign to intermediate and malignant [3-5]. In this study, we describe a case of a 9-year-old child with a malignant epithelioid neoplasm located in the retroperitoneum that harboured a fusion of the EWSR1/CREM genes. Although similar cases have been reported in adult patients, they are very rare in children and may represent a novel type of tumor. The purpose of this report is to underscore the importance of integrating knowledge from the fields of pathological anatomy and genetics in pediatric oncology.

3. Case

A 9-year-old female child presented with a history of nausea and vomiting initially attributed to psychological causes. After 5 months from the onset of symptoms, she developed daily fever, severe abdominal pain, and significant weight loss (13kg in 6 months). She was admitted with a suspected appendicitis, and an abdominal computed tomography (CT) scan revealed a retroperitoneal tumor. An exploratory laparotomy was performed, and a biopsy of a lymph node adherent to the tumor was obtained, revealing an unresectable pancreatic adenocarcinoma. The child was then referred to a pediatric oncology reference center.

On physical examination, the child was in fair overall condition but appeared emaciated and hypochromic, with a flaccid, painless abdomen and normal bowel sounds. There were no palpable tumors or visceromegaly. Additional tests were requested, including

abdominal magnetic resonance imaging which showed conglomerated retroperitoneal and periaortocaval lymphadenopathies extending from the thoracoabdominal transition to the external iliac chains with diffusion restriction, left pieloureteral junction compression, and renal atrophy. Chest CT results were normal. The initial hypotheses were non-Hodgkin's lymphoma and tuberculosis. On reviewing the initial anatomopathological exam slides, the diagnosis was lymph node metastasis of carcinoma. The HE (Hematoxylin-Eosin) exam revealed a neoplasm composed of cohesive cellular blocks with well-defined boundaries, vesicular nuclei, an inconspicuous nucleolus sometimes adhering to the nuclear membrane, with ample cytoplasm sometimes eosinophilic and sometimes slightly vacuolated (Figure 1a). Immunohistochemistry was positive for AE1AE3, CK8/18, CK19, EMA, inibin and focal positive NSE, CD30, vimentin, CEA125, KI67% positive in about 50% of the neoplastic cells, compatible with metastatic carcinoma. The immunohistochemical study showed positive expression of epithelial markers (Figure 1b).

The patient started chemotherapy with cisplatin and 5-fluorouracil but had one episode of low-grade fever daily (37.6-37.8°C) and developed worsening renal function and increased abdominal tumors. The chemotherapy protocol was changed to gemcita-bine and docetaxel, and retroperitoneal radiation therapy was performed at a dose of 200 cGy in 11/25 fractions. The patient showed clinical improvement and pain control, but persistent daily fever. Interleukin 6 (IL6) levels were measured and found to be greater than 5000 pg/ml (normal range 1.5-7 pg/ml). The biopsy material was sent for genomic profiling using next-generation sequencing (NGS), which evaluated 324 genes and introns of 36 genes involved in rear-rangements to detect base substitutions, insertions or deletions, and numerical alterations. The result was positive for EWSR1/CREM fusion. However, the mutational bur-den and microsatellite instability status could not be determined. After four weeks, the patient presented with a left supraclavicular lymph node, marked ascites, pleural effusion, and subcutaneous nodules. She then progressed to respiratory failure and passed away.

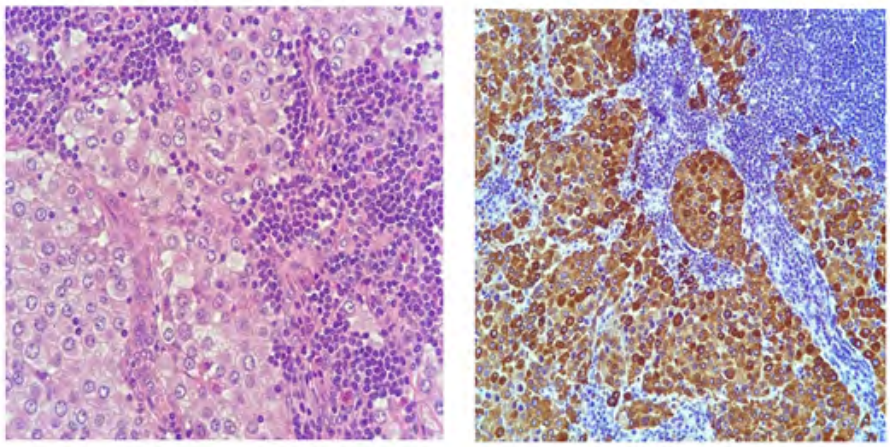

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Figure 1: Histopathological examination (a) HE photomicrograph at 400x magnification of epithe-lioid pattern neoplasia; (b) Positive CK8/18 marker.

4. Discussion

Recurrent chromosomal translocations that form chimeric genes are common in malignant childhood neoplasms. The presence of chimeric transcripts from these translocations can be highly specific molecular markers for a disease entity, which can help in determining the histological type and clinical behavior of the tumor [6]. How-ever, some genetic alterations are common to different histological types, such as EWSR1-CREB1 and/or EWSR1-ATF1, which can be present in angiomatoid fibrous histiocytoma, pulmonary myxoid sarcoma, clear cell sarcoma, and clear cell hyalinizing carcinoma of the head and neck [6, 7]. The EWSR1 (Ewing sarcoma breakpoint region 1) gene is a multifunctional protein expressed in many cell types, located on chromosome 22q12.2. Chromosomal translocations involving this gene and various other transcription factor-coding genes result in chimeric proteins involved in tumorigenesis [3]. The CREB family of transcription factors is composed of the ATF1, CREB1, and CREM genes, and fusions of the EWSR1 gene with CREM, as in the case we describe, are less common and not well characterized [4, 7].

Recently, a new type of neoplasm, classified as malignant epithelioid neoplasm, has been found to have fusions between EWSR1-CREB, including EWSR1-CREM. A literature review described 13 cases with the EWSR1/CREM fusion, with 2 occurring in children and 1 adolescent aged 9, 10, and 14 years. All cases showed at least a focal epithelioid pattern, with 8 cases having a predominant epithelioid histological pattern and the remaining 5 cases showing a mixed histology with areas of epithelioid and spindle or round cell patterns. Five of the 8 cases with a predominant epithelioid pat-tern had foci of rhabdoid tissue. Cysts and lymphocytic infiltrate were also common findings. According to Argani et al., the cases had a morphology similar to angiomatoid fibrous histiocytoma and young adult mesothelioma, which also have EWSR1/FYS-CREB gene fusions. In immunohistochemistry,

all cases showed epithelial differentiation with positivity for cytokeratin and/or EMA. Mesothelial markers such as calretinin and BAP1 were negative, and nuclear WT1 was present in one-third of cases [8]. However, in another study, two adults with intra-abdominal malignant epi-thelioid neoplasms with rearrangement involving the CREM gene showed distinct immunophenotyping. One patient had ALK and keratin-positive immunohistochemis-try, and the other had positive neuroendocrine markers [9]. Rarely, soft tissue sarcomas may present histological characteristics similar to epithelial neoplasms and, morphologically, must be distinguished mainly from carcinomas, mesotheliomas, and thymic tumors [10, 11]. In the case we describe, the initial diagnosis for the child was metastatic carcinoma with an intra-abdominal primary site in the pancreas. In Argani et al.'s review, of the 13 cases described, 10 tumors were in-tra-abdominal and involved the peritoneum, omentum, mesocolon, or retrovaginal pouch. Two children had lesions, with one being intra-abdominal and involving the retrovaginal space, and the other located in the lower limb [8]. Our patient is the third case described as epithelioid neoplasm with fusion of EWSR1/CREM genes in children.

In the patient described here, the tumor was located in the periaortocaval retro-peritoneal region, which is a rare site for epithelioid neoplasms with EWSR1/CREM gene fusion. The behavior of the tumor was aggressive and it was refractory to chemotherapy, eventually leading to metastases in the pleura, peritoneum, and lymph nodes, which is consistent with other cases reported in the literature [3, 7]. In tumors with EWSR1/CREB gene fusion, there are reports that interleukin 6 (IL6) levels may be elevated and may promote tumor growth through autocrine stimulation, with symptoms suggestive of a paraneoplastic syndrome, characterized by fever, weight loss, and abdominal pain [12, 13]. Potter et al. reported a case of a 3-year-old patient with fibrous histiocytoma of the extremity with EWSR1/CREB1 fusion who had a paraneoplastic syndrome and was treated with tocilizumab, an IL6 receptor inhibi-tor. The patient showed improvement in symptoms and a partial response of the tumor [14]. Our patient had very high IL6 levels and developed fever and weight loss. Although she may have benefitted from an IL6 inhibitor, the medication was not obtained in time. Radiotherapy was the only treatment that temporarily relieved symptoms.

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5. Conclusion

In summary, we have described a case of a retroperitoneal epithelioid neoplasm with EWSR1/CREM gene fusion in a pediatric patient. The conclusive diagnosis was achieved via histopathological evaluation, complemented by immunohistochemical and molecular biology analyses. Our report contributes to the knowledge of the clinical and biological characteristics of this rare tumor in children. Research of the genomic profile of tumors with epithelial differentiation may lead to the identification of a new group of malignant tumors related to EWSR1 gene fusion with CREB family genes, which could potentially aid in therapeutic planning.

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