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Case Report

Aggressive Pediatric Adrenal Cortical Carcinoma With a Novel Translocation t(20;22) and intergenic fusion of MN1 and ZNF341: A Case Report and Literature Review

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Abstract:

Caroli disease involves several different entities in contrast to Caroli syndrome. We herein report two cases of congenital localized dilatation of the intrahepatic bile ducts exhibiting a unique morphology distinct from other types of Caroli disease. Specifically, the dilatation was limited to the second- and third-order intrahepatic bile ducts, and the dilated bile ducts abruptly connected to normal-sized ducts on both the upstream and downstream sides. Both cases are prenatally diagnosed and have been asymptomatic for nearly a decade. Nine other cases were identified in the English and Japanese literature, suggesting that this is a specific subtype of Caroli disease.

Key words: adrenal cortical carcinoma; MN1; ZNF341; t(20;22)

Introduction

Adrenal cortical carcinoma (ACC) is a rare pediatric malignancy with a reported incidence rate of 0.2 - 0.3 new cases per 1 million children per year [1]. ACC is a very aggressive neoplasm with a dismal prognosis and a 5-year overall survival rate of 16-44% [4]. Majority of ACCs are sporadic and unilateral but 2-6% are reported to be bilateral and associated with predisposition genetic syndromes such as Li-Fraumeni syndrome, multiple endocrine neoplasia type 1, Beckwith-Wiedmann syndrome and the Carney complex [5]. The most common site of distant metastasis in orders are the lungs, liver, peritoneum, lymph nodes, and bones [6]. A retrospective study led by Gupta et al. in 2018 has showed that the presence of metastases in patients with adrenal cortical carcinoma is an independent poor prognostic factor [7, 8]. For pediatric patients with metastatic adrenal cortical carcinoma, the 5-year survival rate is approximately 20% [9]. Differentiating ACC from other tumor metastases to the adrenal gland can be very challenging especially in pediatric populations. as the histologic features of ACC are highly variable. Microscopic examination of ACC often demonstrates tumor contains nuclei that are ranging from bland to highly atypical/pleomorphic with clear to eosinophilic cytoplasm in the setting of variable mitotic figures. Moreover, the histologic features of malignant ACC in adults may not be well correlated with aggressive disease seen in the children. The treatment of choice for ACC is usually radical surgical resection with clear margin. Although, neoadjuvant chemotherapy can be used in the setting of incomplete resection, metastatic disease, or ineligibility for surgery. In case of metastasis, ACC has dismal prognosis and biomarkers such as TOP2A, EZH2 and BARD1 could serve as poor prognostic indicators [10]. Our case demonstrates two additional genes, MN1 and ZNF341, which may have potential to predict the clinical course of this devastating disease.

Case presentation

The patient was a 3-month-old, ex-36 weeks, otherwise healthy male who presented with multiple, growing masses on the head, chest, and back within a three-week period. Initially dismissed as bug bites, then the masses became protuberant and erythematous, with varying consistencies and texture. Subsequently smaller skin-colored lesions also appeared on the infant's chest, back, and lower extremities, which exhibited rapid growth. Extensive whole-body imaging were done which showed multiple lesions of the calvarium, with the largest measuring 3.8 x 3.3 x 2.7-cm and causing regional left cerebellum mass effect **(Figure 1A).** There was also a 4.8 x 3.8 x 3.2-cm destructive mass involving the right mandibular body and ramus **(Figure 1B).** Further imaging of the abdomen and pelvis revealed a large suprarenal mass, multiple pulmonary nodules, destructive changes in the left ninth rib, and ill-defined lucency of the inferior margin of the **sternum (Figure 1C-D).** The patient was admitted to the oncology service for further workup with the initial impression of metastatic neuroblastoma. A metaiodobenzylguanidine (MIBG) scan was done, but the results were inconclusive.

The left forehead mass was biopsied and microscopic sections showed sheets of poorly differentiated tumor cells with high mitotic activity and necrosis imprinting a round blue cell tumor **(Figure 2-A).**

An extensive panel of immunostains performed shows the tumor cells are immunoreactive for SF-1 (strong and diffuse), calretinin (focal), Melan-A, synaptophysin, CD56, and PGP9.5 and are negative for Phox2B, inhibin, EMA, SALL4, AE1/AE3, desmin, myogenin, Myo-D1, NKX2.2, CD99, SATB2, WT-1, CD43, S100, SOX10, and CD34 with high Ki67 proliferation index (~60%) and retained nuclear expression of INI-1, BRG-1 and RB to suggest metastatic ACC **(Figure 2-B-D).** Due to the complexity of the case and unusual presentation, the case was sent for second opinion to two different institutions (Children's Hospital of Los Angeles and Texas Children's Hospital) which both concurred with the diagnosis of metastatic ACC. Fluorescent In-Situ Hybridization (FISH) study showed no evidence of EWSR-1 or SYT gene rearrangements or MYC-N gene amplification. While waiting for the second opinion, the patient underwent resection of the supra-adrenal mass. The morphology and immunohistochemical features of the resection were similar to the patient's previous biopsy. Next-generation sequencing demonstrated an intergenic fusion of unknown significance: t(20;22) MN1::ZNF341, which to our knowledge has not been reported previously in any ACC or other tumors.

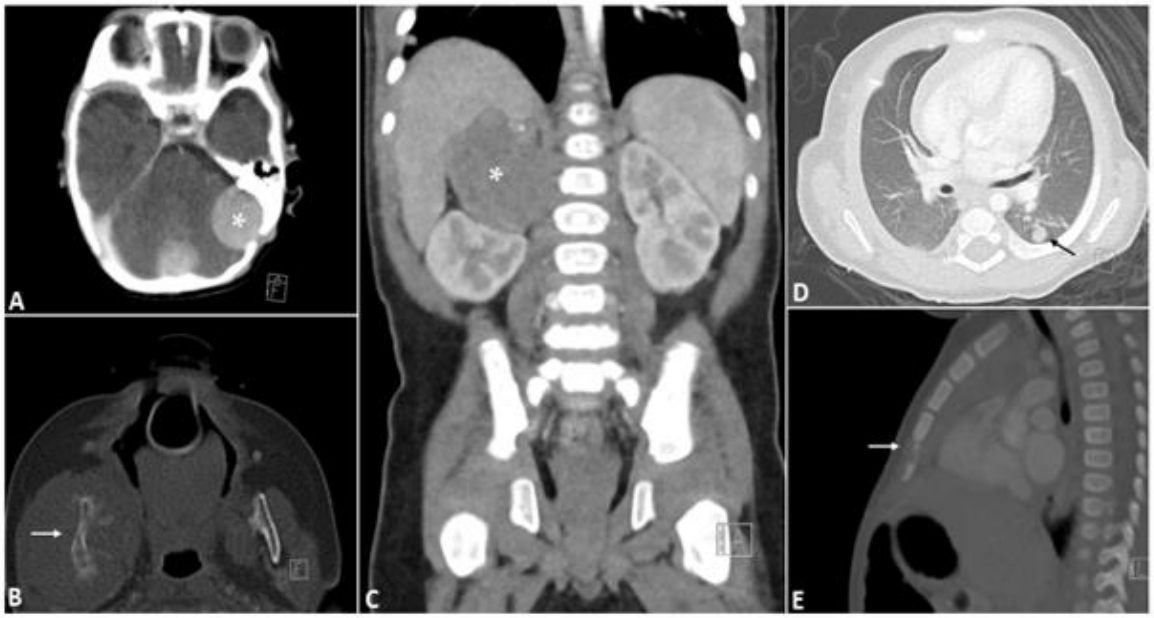

Figure 1. (A) Axial CT image of the brain with contrast demonstrates a large enhancing mass in the left posterior fossa abutting the lambdoid suture (*) with regional mass effect on the left cerebellum. Additional posterior fossa mass is also seen at the midline. (B) Axial CT image of the face with contrast in bone window demonstrates a destructive mass involving the right mandibular body and ramus with aggressive sunburst periosteal reaction and associated soft tissue mass (white arrow). (C) Coronal CT image of the abdomen and pelvis with contrast demonstrates a well-marginated lobulated partially calcified right suprarenal mass with mass effect on the upper pole of the right kidney (asterisk). The mass abuts the inferior margin of the liver without definite invasion. (D) Axial CT image of the chest with contrast in lung window demonstrates a round metastatic pulmonary nodule in the left lower lobe (black arrow). (E) Sagittal CT image of the chest in bone window demonstrates a lytic lesion involving the anterior and inferior sternum with associated soft tissue mass (white arrow).

Figure 2.

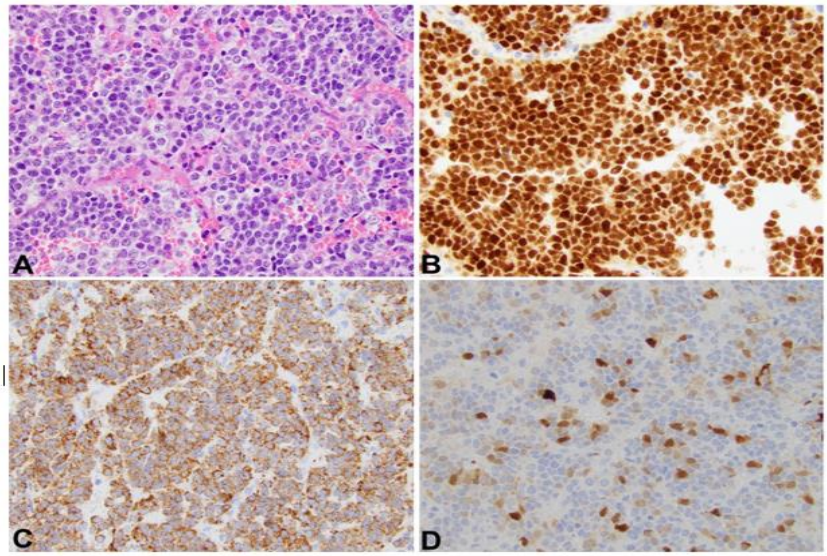

Figure 2(A). The scalp mass biopsy shows sheets of poorly differentiated tumor cells characterized by large, round, nuclei with granular chromatin, inconspicuous nucleoli and scant cytoplasm (Hematoxylin and Eosin stain, magnification 200x). The tumor cells demonstrate immunohistochemical reactivity for **(B)** SF-1 **(C)** Melan-A, and **(D)** Calretinin, patchy (B-D, magnification x200).

The patient had initially begun treatment per ANBL0531 for presumed neuroblastoma but then was changed for subsequent cycles to treatment per modified ARAR0332 for ACC. He initially responded to treatments but then progressed and continued to decline despite trials of other treatment regimens. While hospitalized in the intensive care unit, he experienced a sudden deterioration with fixed pupillary dilation. Imaging showed worsening intracranial bleeding, increased cerebellar mass size, innumerable hemorrhagic metastases, and a spinal tap was positive for spinal metastases. The family decided to withdraw life support.

Discussion

ACC is a rare malignant epithelial neoplasm of the adrenal cortex. ACC has a poor prognosis, with the estimated 5-year survival rate ranges from 16 to 44% [11-13]. The prognosis drops to 13% in patients with distant metastasis [13, 14]. Nearly 40% of the patients with adrenal cortical carcinoma are known to have distant metastasis at the time of diagnosis. Currently, four well-described cases of infant adrenal cortical carcinoma (ACC) have been reported [15-18]. **Table 1** summarizes all case reports of ACC in infancy. Here, we report a fifth case of ACC in infancy. This case reports a new translocation, t(20;22) MN1::ZNF341, and its association with a difficult-to-define, poorly-differentiated malignant neoplasm that caused the rapid decline of a patient.

Age (MO)/Sex	Presentation	Metastasis	Treatment	Follow-up	Reference
2/M	6-cm left adrenal mass	Right lung	Adrenalectomy + mitotane	Alive; WED at 15 Y	[15]
3/M	3-cm right adrenal mass	Absent	Adrenalectomy only	Alive; WED at 6 MO	[16]
4/M	9-cm left adrenal mass	Absent	Adrenalectomy only	Alive; WED at 7 Y	[17]
6/F	5-cm right adrenal mass	Absent	Adrenalectomy only	Alive; WED at 2 Y	[18]

Published cases of infantile adrenal cortical carcinoma

Abbreviation: F, female; M, male; MO, months; WED, without evidence of disease; Y, years

In terms of treatment for ACC, radical surgical resection is generally performed for stage I to stage III ACC. Stage IV ACC is treated with radical resection in conjunction with adjuvant mitotane, which is a synthetic derivative of insecticide dichlorodiphenyltrichloroethane [19]. Chemotherapy regimens including a combination of etoposide, doxorubicin, and cisplatin in addition to mitotane have been reported for incompletely resected ACC, for metastatic disease, or for patients who are not eligible for surgery.

The molecular genetics with regards to tumorigenesis of ACC remain poorly understood [20]. Literature has shown that up to 4% of ACC can be attributed to predisposition syndromes such as Li-Fraumeni syndrome, multiple endocrine neoplasia type 1 and Beckwith-Wiedemann syndrome. In addition, cases have shown sporadic ACC is mostly associated with somatic mutation of TP53 gene. Interestingly, a small subset of ACC is also shown to have somatic mutations in the β-catenin gene CTNNB1.

Our case is a diagnostically challenging case and pathological evaluation is reinforced with supplemental molecular findings. Interestingly, this case stems from an aberrant novel translocation t(20;22), resulting in an intergenic fusion of MN1 and ZNF341, which led the patient to succumb roughly four months after initial diagnosis due to rapid proliferation of the cancer. MN1 is a transcriptional activator that regulates the expression of TBX22 in palate development and fusion of the palatal shelves [21]. In addition, MN1 induces expression of the osteoclastogenic cytokine

TNSF11/RANKL and is responsible for normal functioning and maturation of osteoblasts in the calvarium [22]. MN1 gene mutations are found in rare cases of malignant peripheral nerve sheath tumor that are associated with von Recklinghausen's disease. [23]. Interestingly, the overexpression of MN1 in glioma is shown to be associated with low grade gliomas and absent in high grade gliomas [24]. The role of overexpression or translocations of MN1 was found to be involved in worse prognosis among patients with acute myeloid leukemia although clear elucidation of molecular mechanism is still needed [25]. On the other hand, ZNF341 is a nuclear zinc finger transcription factor that regulates the expression of the protein STAT3, which regulates human immune homeostasis [26]. Limited literature has shown that ZNF341 deficiency has been associated with impaired DNA repair mechanisms, which led to various malignancies [27]. Thus, the aberrant translocation of ZNF341 indirectly causes immunodeficiency and can be partially attributable for tumorigenesis. In our case, the presence of a novel translocation t(20;22) in the setting of metastatic ACC encourages more in-depth studies to elucidate the molecular pathogenesis of metastatic ACC in hopes of finding more targeted therapy to achieve effective treatment

Conflict of interests:

The authors declare that there is no conflict of interests regarding the publication of this article and there have been no significant financial contributions for this work that could have influenced its outcome.

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