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Case Report

Histiocytosis Presenting as Bilateral Adrenal Masses: A Case Report

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Keywords

Adrenal mass · Histiocytosis · Bilateral adrenal masses · Adrenal histiocytosis

Abstract

Introduction: Adrenal masses are a rare diagnosis in children, with bilateral masses even less common. At present, appearance of the mass on imaging and histology can give important clues to the diagnosis; however, there is significant overlap in 10–30% of cases and it can be difficult to distinguish benign from malignant adrenal masses. As a result, the clinical presentation remains a large part of the diagnostic process, as well as thorough endocrinology evaluation to determine if the tumor is functional versus nonfunctional. ***Case Presentation:*** We present a recent case of bilateral adrenal masses in a pediatric patient at our institution, with an unusual diagnosis of histiocytosis. ***Conclusion:*** In this case, the diagnosis was unclear, until genetic testing and pathology allowed for expedient diagnosis and targeted therapy for this patient. We hope that presenting this case will increase physician awareness of this condition and expedite diagnosis and treatment in other patients with this rare presentation.

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Introduction

Bilateral adrenal masses are an uncommon finding, with a vast differential diagnosis, which includes metastatic disease (renal, lung cancer, melanoma), lymphoma, pheochromocytoma, Cushing's syndrome, congenital adrenal hyperplasia, primary aldosteronism, and infections. As such, clinically they present with a wide degree of clinical symptoms, from asymptomatic to hypocortisolism to signs of hormone excess.

A single-center study in India in 2016 found that of 74 patients with bilateral adrenal masses, the most common diagnoses were pheochromocytoma (40%), followed by tuberculosis (27.1%), primary adrenal lymphoma (10%), metastases (5.7%), non-functioning

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adenomas (4.3%), primary bilateral macronodular adrenal hyperplasia (4.3%), and other rare masses (8.6%) [1]. There are currently no studies in the literature that have examined the prevalence of bilateral adrenal masses in children.

At present, there is no reliable tool to help distinguish the type of adrenal mass based upon imaging alone. Cysts, myelolipomas, and adrenal hemorrhage have characteristic findings on CT and can be easily excluded. Use of Hounsfield units can help distinguish some adenomas from carcinoma – if a mass is less than 10 Hounsfield units, the likelihood of adenoma is increased [2]. However, CT scans are still unable to reliably differentiate functional versus nonfunctional masses or benign versus malignant masses. MRI is more helpful, with pheochromocytomas usually more hyperintense and adenomas with a lower signal on T2-weighted images. Chemical shift MRI is increasingly used to differentiate benign from malignant adrenal masses; however, overlap still occurs in 10–30% of cases [3]. PET/CT is also increasingly being used for characterization of adrenal masses, however mainly as an adjunct to other imaging modalities [4].

FNA biopsy can be used to diagnose adrenal masses, however is not recommended as part of standard evaluation. Additionally, it is crucial to exclude pheochromocytoma prior to biopsy. As a result, FNA is most often used in patients with a known extra-adrenal mass. However, on review of histology it is often difficult to differentiate normal adrenal tissue from adenoma or well-differentiated carcinoma [2].

Because of this overlap in the appearance of benign and malignant adrenal masses on CT and MRI, often the clinical picture is largely responsible for leading the physician to a diagnosis. If an adrenal mass is functioning, the patient may have findings of hypercortisolism, virilization, or hypertension and have characteristic hormone levels that help guide the clinician to a diagnosis of adrenocortical carcinoma (ACC). Here we discuss a case that we hope will be useful to future clinicians presented with the conundrum of diagnosing bilateral adrenal masses in children.

Case Presentation

A 17-year-old Vietnamese female presented to the emergency department with chest pain, several weeks of fatigue, decreased appetite, a dry cough, and unintentional weight loss over 2 months. Her vital signs were normal and the physical exam was without virilization or cushingoid features. Physical exam was notable for clubbing and right flank tenderness. Initial laboratories obtained showed a normocytic anemia and normal electrolytes. CT-angiography of the chest revealed a 9.2 × 8 × 7.4 cm large heterogeneous hypervascular mass in the right lower lung, a similar-appearing 7.1 × 5.4 × 6.9 cm heterogeneous mass in the left adrenal gland, and a 3.4 cm hypodense mass in the right adrenal gland (shown in Fig. 1, 2). CT abdomen and pelvis also showed a 1 cm lesion abutting the dorsal pancreas and a right adnexal enhancing mass.

Further laboratory testing showed normal tumor markers: CA 19-9, AFP, beta-Hcg, CA 125, and CEA. Dopamine, epinephrine and norepinephrine levels were normal. Urine metanephrine to creatinine ratio, free metanephrines, and normetanephrines were normal. HVA and VMA were done for neuroblastoma screening and were in normal ranges. Testing for *Echinococcus*, *tuberculosis*, and *Coccidioides* was negative. Endocrine workup was normal with 17-hydroxyprogesterone at 81 ng/dL, aldosterone 2.0 ng/dL, renin 1.5 ng/mL/h, DHEAS 37 μg/dL, testosterone 14 ng/dL, progesterone less than 10 ng/dL, ACTH 29 pg/mL, and AM cortisol 18.2 μg/dL (shown in Table 1). She underwent interventional radiology-guided biopsy of the left adrenal mass and was discharged.

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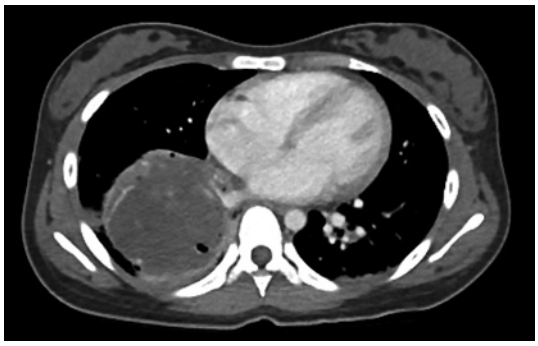

Fig. 1. CT scan from November 2021 demonstrating large left adrenal mass and right adrenal mass and right lower lobe mass.

She was readmitted for chemotherapy after preliminary pathology from the adrenal mass returned ALK positive. Ancillary staining of the mass showed it was positive for ALK-1, WT1, and D240 (Fig. 3), and it was sent to Mayo laboratory for consultation. MRI brain showed abnormal clival signal consistent with metastatic disease but no evidence of metastasis. MRI spine did show evidence of spinal metastasis. PET scan showed diffuse bony lesions. Due to evidence of metastasis and acute onset of hypoglossal nerve deficit, she received a 2-day course of palliative radiation therapy (8 Gy) to clival region and C4–C7. She was started on crizotinib, an ALK/ROS1 inhibitor, in December 2021. During her hospital stay, she endorsed persistent cough, headaches and also developed blurry vision after starting crizotinib, possibly a side effect of the medication. During this hospitalization, the final pathology from Mayo laboratory was received and was confirmed as a malignant ALK-positive neoplasm harboring DCTN1-ALK fusion transcript, likely representing ALK-positive histiocytosis. Immunohistochemistry performed showed CD163-positive cells, as well as scattered WT-1 positivity. Next-generation sequencing demonstrated the DCTN1-ALK fusion transcript (Fig. 4). Follow-up CT abdomen and pelvis obtained 1 week after starting crizotinib showed a decrease in the size of lung and adrenal masses (shown in Fig. 5, 6), with lung mass now 7.9 × 7.5 cm (previously 8.2 × 8), left adrenal mass now 7.6 × 5.6 (previously 8.2 × 6.2), and right adrenal mass 1.1 × 1.0 cm (previously 3 × 2 cm). She was discharged on crizotinib 400 mg BID.

ALK-positive histiocytosis was originally reported in infants but more recently has been reported in older children and young adults, particularly of Asian origin. Most of these cases have been reported to have a KIF5B-ALK fusion mutation; however, there are a few reports of DCTN1-ALK fusion that was seen in our patient. DCTN1-ALK fusion mutations have also been rarely reported in non-small cell lung cancer, inflammatory myofibroblastic tumor, spindle cell variant of epithelioid cell histiocytoma, and juvenile myelomonocytic leukemia. Tumors with ALK fusions have been shown to respond to ALK-inhibitor therapy.

She was seen a week later in oncology clinic, and the final pathology report showed the rare diagnosis of metastatic DCTN1-ALK fusion-positive histiocytosis. After 3 weeks on crizotinib, her hypoglossal nerve deficit resolved and headaches and cough had significantly improved. Follow-up PET scan 2 months later showed resolution of lesion in left occipital condyle and decreased avidity of the other bony lesions. The right lung mass and left adrenal mass had further decreased in size, and the right adrenal lesion was no longer seen. She continued on the same dose of crizotinib with good response. She had significant improvement in extracranial lesions on crizotinib, but May 2022 scans showed a small CNS lesion despite improved intracranial disease, suggesting sanctuary site disease on crizotinib. She was switched to lorlatinib, which has documented superior CNS penetration. Follow-up MRI brain 2 months later showed resolution of the left frontal lobe lesion. The most recent scan done in August 2022 demonstrated continued improvement while on lorlatinib, with right lower lobe mass and left adrenal mass continuing to decrease in size.

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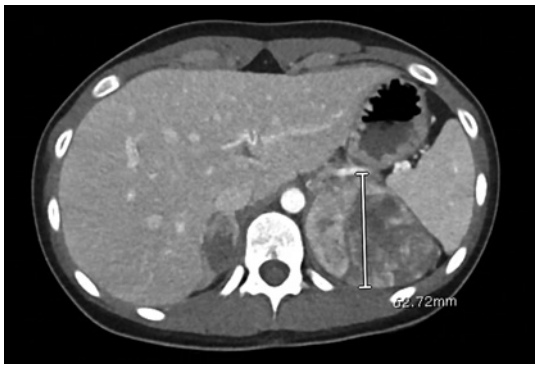

Fig. 2. CT scan from November 2021 demonstrating large left adrenal mass and right adrenal mass and right lower lobe mass.

Table 1. Laboratory evaluation obtained in our patient with bilateral adrenal masses

Cortisol (07:24 AM)	18.2 μg/dL (3–27)	Free normetanephrines	<0.2 nmol/L (<0.9)
ACTH	29 pg/mL (6–48)	Free metanephrines	<0.2 nmol/L (<0.5)
Aldosterone	2.0 ng/dL (<31)	Norepinephrine	244 pg/mL
Renin	1.5 mg/mL/h (0.167–5.38)	Epinephrine	<20 pg/mL
DHEA-S	37 μg/dL (44–248)	Dopamine	<10 pg/mL
17-OH progesterone	81 ng/dL (20–265)	HVA	3.9 mg/g Cr (1–12)
Total testosterone	14 ng/dL (20–38)	Urine metanephrines to creatinine ratio	226 μg/g (180–700)
Progesterone	<10 ng/dL (<10–2,555)	VMA	3.6*3 mg/g Cr (1–6)
CA 19-9	12 μ/mL (<34)	CEA	0.4 ng/mL (<3)
Beta-HCG	<0.6 IU/L (<1)	CA 125	24 μ/mL (<46)
AFP	<2.0 ng/mL (2–12)	Vitamin D 25-OH	27.2 ng/mL

Discussion and Conclusions

Adrenal neoplasms are rarely seen in pediatric patients. In children, pheochromocytoma and ACC are the most common non-neurogenic adrenal tumors. ACC constitutes less than 1% of childhood malignancies, with a worldwide annual incidence of 0.3 per million children under the age of 15. Pheochromocytoma is also found in less than 1% of all observed pediatric malignancies and is even less common with an incidence of 0.2–0.3 per million children. Pheochromocytoma is associated with an inherited genetic syndrome in 80% of cases [5].

Pheochromocytomas typically present with symptoms of hyperadrenergic spells and sometimes abdominal pain, unless they are detected on screening for MEN syndrome. They are bilateral in about 20% of cases in children, with 80% located in the adrenal gland and 20% found in the upper abdomen [6]. When bilateral, they have been found to have a greater familial and syndromic association than unilateral pheochromocytomas. Syndromes with a higher likelihood of bilateral pheochromocytoma include multiple endocrine neoplasia type 2, Von Hippel-Lindau disease, neurofibromatosis type 1, tuberous sclerosis, Carney triad, and Sturge-Weber syndrome [7]. Pheochromocytomas typically present as larger hypervascular masses and can appear similar to adenomas. They are extremely variable in appearance.

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Ancillary stains/Studies for diagnostic and/or Therapeutic Clarification (with appropriate controls):

Block	Stain/Study	Method	Results	Technical site
2A	Desmin	IHC	Negative	CHOC
2A	PHOX2B	IHC	Negative	CHOC
2A	S100	IHC	Negative	CHOC
2A	ALK-1	IHC	Cytoplasmic positivity	NeoGenomics
2A	PAX8	IHC	Negative	NeoGenomics
2A	HMB45	IHC	Negative	NeoGenomics
2A	SMA	IHC	Negative	NeoGenomics
2A	SF-1	IHC	Negative	NeoGenomics
2A	CD1A	IHC	Negative	NeoGenomics
2A	TFE3	IHC	Negative	NeoGenomics
2A	Langerin	IHC	Negative	NeoGenomics
2A	Synaptophysin	IHC	Negative	NeoGenomics
2A	Pancytokeratin	IHC	Negative	NeoGenomics
2A	Melan A	IHC	Negative	NeoGenomics
2A	WT-1	IHC	Positive	NeoGenomics
2A	D240	IHC	Positive	CHOC
2A	INI-1	IHC	Retained nuclear expression	NeoGenomics

Fig. 3. Ancillary staining from the adrenal mass.

Paragangliomas can occur in association with pheochromocytomas and as a part of familial syndromes so should be evaluated for when a pheochromocytoma is found.

As their name suggests, ACCs arise from the adrenal cortex and as such can be secretory about 50% of the time. These are bilateral 10% of the time and usually present with symptoms of hypercortisolism or virilization [6, 7]. Adrenal carcinomas have a heterogeneous appearance, often with central necrosis and calcifications.

Other adrenal masses to consider in children include lymphoma, adenomas, myelolipomas, neuroblastoma, or metastasis. Non-Hodgkin lymphoma is the most likely lymphoma to involve the adrenal gland and is bilateral in nearly 50% of cases. Two-thirds of patients with bilateral involvement have been reported to have adrenal insufficiency (AI). In children, adrenal adenomas typically present with symptoms of cortisol or androgen excess and in up to 20% of cases may be bilateral [6]. They may be associated with Li-Fraumeni, Beckwith-Wiedemann, and hemihyperplasia syndromes, as well as multiple endocrine neoplasia type 1, McCune-Albright syndrome, Lynch syndrome, familial adenomatous polyposis, and congenital adrenal hyperplasia (CAH) [5]. Rarely, adrenal adenomas and carcinomas are found in cases of untreated CAH. Myelolipomas are benign adrenal tumors composed of a mix of adipose and hematopoietic tissues. They rarely are associated with endocrine disorders such as CAH, Cushing syndrome, Conn syndrome, and Nelson syndrome. They can be bilateral in up to 13% of cases. Patients with CAH who are poorly compliant to treatment have a higher risk of myelolipomas. Neuroblastomas involving the adrenal medulla are the most common pediatric adrenal mass, however are bilateral in less than 10% of cases [6]. Patients with bilateral neuroblastoma are more likely to have a familial association and to present at an earlier age, usually less than 6 months. These masses are also more likely to have higher tumor staging at time of diagnosis [7].

The adrenal glands are a common site of metastasis from lung, breast, gastric, renal, pancreatic, and colon carcinomas, as well as melanomas and lymphomas. Around 90% of adrenal metastasis is carcinoma, which can be bilateral in nearly 50% of cases. An exception to

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Result

Referral information: adrenal, ALK-positive epithelioid cell tumor

The following fusion was identified:

DCTN1 - ALK

The specific gene transcript(s) (described by RefSeq accession number) involved in the identified fusion/transcript variant(s) are unknown.

Fusion/transcript variant junction locations and mutation nomenclature are based on the following RefSeq accession number(s) (build GRCh37 (hg19)): NM_001190836 and NM_004304.

The fusion/transcript variant junction location and the corresponding genomic coordinates within the DCTN1 gene occur in exon 23 at genomic position chr2:74592202 and within the ALK gene occur in exon 20 at genomic position chr2:29446394.

Fig. 4. Final pathology identifying the DCTN1-ALK fusion gene.

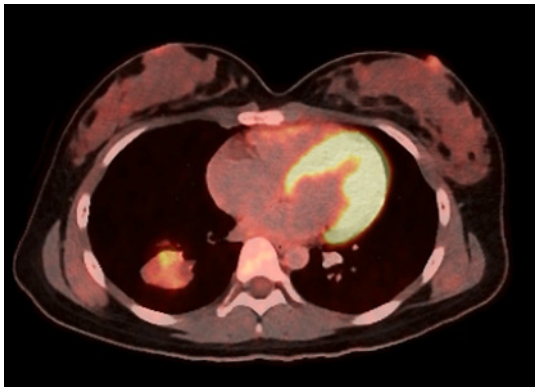

Fig. 5. PET scan from August 2022 shows left adrenal mass has significantly decreased in size, as well as right lung mass.

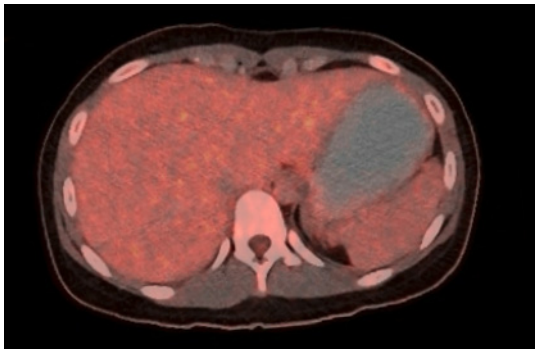

Fig. 6. PET scan from August 2022 shows left adrenal mass has significantly decreased in size, as well as right lung mass.

this is lung cancer in which metastasis is bilateral in only 3% of cases. Metastases from carcinoma and melanomas can be similar in appearance on imaging to pheochromocytoma, however may have ill-defined margins as a distinguishing feature [8].

It is also important to consider infections such as tuberculosis, histoplasmosis, and blastomycosis, which all can result in bilateral adrenal enlargement and eventually cause gland atrophy and calcification. Extensive involvement results in AI. Worldwide, tuberculosis is the most common cause of Addison disease [6].

A diagnosis to consider with bilateral adrenal involvement is diffuse cortical hyperplasia, which is seen in 45% of cases of Cushing syndrome, with 3% being nodular in appearance. In ACTH-dependent cases, adrenal hyperplasia occurs due to exogenous or pituitary

overproduction of ACTH. In ACTH-independent cases, the source of hypercortisolism is usually a functioning adrenal adenoma or carcinoma [6]. Hypercortisolism can also be seen in rare cases of primary bilateral macronodular adrenal hyperplasia or primary pigmented nodular adrenal dysplasia.

Adrenal hemorrhage may also be bilateral in up to 20% of cases. This is the most common adrenal "mass" found in neonates. Acutely these are hyperattenuated, however can eventually lead to adrenal calcifications or pseudocyst formation. Adrenal hemorrhage does not commonly cause AI. Adrenal hypoperfusion and infarction on imaging also have their own distinct appearance on imaging and can demonstrate bilateral involvement. In children, it is also important to be aware that gastric fundal diverticulum, vascular abnormalities, extralobar pulmonary sequestration, and extramedullary hematopoiesis can mimic the appearance of adrenal masses [7].

To our knowledge, this is the first reported case of bilateral adrenal masses secondary to the rare diagnosis of metastatic DCTN1-ALK fusion-positive histiocytosis. By reporting this case, we hope to add to the sparse literature on bilateral adrenal masses. The differential diagnosis for bilateral adrenal diagnosis is incredibly broad, and different types of adrenal masses may share similar characteristics and appearance on imaging, necessitating thorough endocrinology, oncology, and infectious disease evaluations. In this case, genetic testing of the adrenal mass identified the DCTN1-ALK fusion gene, and she was able to quickly be started on targeted therapy with ALK-inhibitors. She responded well to crizotinib and lorlatinib, and as a result will likely be able to avoid adrenal resection. In adult lung cancer studies, next generation ALK inhibitors can induce CNS response after CNS progression on crizotinib. The plan moving forward will be to repeat scans in about 6–8 weeks to assess response to lorlatinib. If there is resolution of the small CNS disease, then decision can be made on whether right lower lobectomy is indicated based on the scans and whether there is still residual PET avid disease in the lungs. We hope that by reporting this interesting case, we can increase physician awareness of this condition and add yet another possibility to the differential diagnosis for bilateral adrenal masses in children.

The CARE Checklist has been completed by the authors of this case report, included as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535195).

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We appreciate the collaboration of Dr. Cavannaugh, CHOC Oncology Fellow, in this case report.

Statement of Ethics

Informed consent was obtained from the parent of the patient for publication of the information presented in this manuscript, including the case and accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Daina Dreimane, MD, contributed to this case report through mentorship, critical review, and editing. Julianne Bullock, DO, authored this case report and Corey Cavannaugh, MD, contributed his expertise in oncology as well as authoring a section of this paper. Written informed consent was obtained from the parent for publication of this case report and any accompanying images.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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