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ORIGINAL ARTICLE

NUT midline carcinoma: an imaging case series and review of literature

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Abstract
Background NUT midline carcinoma is a rare and aggressive tumor that has primarily been reported in children and young adults. The tumor is characterized by a rearrangement on the nuclear protein in testis (NUT) gene, located on chromosome 15q14, resulting in the BRD4-NUT fusion oncogene. This carcinoma most commonly presents in the midline and displays an invariably lethal clinical course.
Objective To highlight the imaging features of NUT midline carcinoma.
Materials and methods IRB approval was obtained for chart review. We retrospectively reviewed the chart and imaging studies of three children. All three cases were diagnosed by karyotyping and confirmed by fluorescence in situ hybridization (FISH). Cross-sectional imaging including CT, MRI and, in one patient, PET was available for review.
Results Two out of three children presented with midline and multifocal disease. The third case had a medial left thigh mass and no metastatic disease at initial presentation. The common imaging features include heterogeneous low density on CT and T1 hypointensity and low-level T2 hyperintensity on MRI with heterogeneous enhancement. All cases were confirmed pathologically and by molecular studies.
Conclusion NUT midline carcinoma usually presents in the midline, either in the head, neck or chest. We present three cases with the bulk of the tumor below the diaphragm, which is seen in the minority of patients with NUT midline carcinoma, according to the available literature. Metastatic disease is common at initial presentation and can be quite extensive. The most striking feature of this disease is its aggressive nature with exponential interval growth of tumor.

Keywords NUT midline carcinoma · Imaging · Radiology · Children

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Introduction

NUT midline carcinoma is a rare but increasingly recognized highly lethal malignancy that results from a chromosomal translocation, t(15;19) with BRD4-NUT oncogene expression. There is very little literature regarding the imaging appearance of this malignancy, with only one prior case report in the radiology literature to our knowledge. This disease has been described primarily in the pathology and oncology literature, including two of our three patients reported by Shehata et al. [1] in the pathology literature. We report the imaging findings of three children who presented to our children's hospital with poorly differentiated carcinomas expressing the NUT oncogene.

Materials and methods

IRB approval was obtained for chart review. We retrospectively reviewed the chart and imaging studies of three children including a newborn, a 2-year-old and a 14-year-

old. All three cases were diagnosed by karyotyping and confirmed by fluorescence in situ hybridization (FISH) to have the classic BRD4-NUT fusion rearrangement. Cross-sectional imaging including CT, MRI and, in one patient, PET was available for review.

Results

Case 1 An African-American newborn boy presented with a left supraorbital mass at birth that was initially thought to represent a hemangioma. Over a period of 3 weeks, the mass grew exponentially, resulting in the boy's inability to open his left eye. Contrast-enhanced CT scan of the head (CTDI not available, outside exam) demonstrated a heterogeneously enhancing left supraorbital mass with calcifications (Fig. 1), which prompted further work-up with contrast-enhanced CT scan of the chest, abdomen and pelvis (CTDI 6.46 mGy). There was extensive disease in the chest, abdomen and pelvis including a large ill-defined right suprarenal mass extending across the midline to the left suprarenal space, a large mass in the central pelvis between the bladder and rectum and multiple bilateral renal cortical-based hypodensities (Fig. 1). A single small hypodense mass was also identified in the liver. There were several subcutaneous and bilateral pulmonary nodules (Fig. 1). The adrenal and renal masses were primarily hypodense to the liver and renal parenchyma, with mild heterogeneity. The pelvic masses and subcutaneous masses were primarily isodense to the soft tissues. Follow-up MRI of the brain and spine additionally demonstrated a left parotid mass as well as multiple intracranial (Fig. 2) and intraspinal metastatic lesions (Fig. 3). On MR, lesions were low to isointense in signal intensity on T1, heterogeneously hyperintense on T2, and heterogeneously enhancing on postcontrast images. Intracranial lesions demonstrated restricted diffusion. Given the age of the boy, extensive disease, suprarenal location of the largest lesion and presence of calcification in the periorbital lesion, our primary differential consideration was metastatic stage IVs neuroblastoma; other possibilities included rhabdomyosarcoma or other sarcomatous lesions.

Pathological evaluation of the subcutaneous nodules revealed undifferentiated carcinoma with squamous differentiation. Chromosomal analysis demonstrated a translocation between the long arm of chromosome 15 and the short arm of 19 t(15;19), which was confirmed by FISH. Thus, a diagnosis of NUT midline carcinoma was made. In the interim, there was relentless progression of initial lesions as well as new metastatic foci. A ventricular shunt catheter was required for obstructive hydrocephalus secondary to subarachnoid hemorrhage. Subsequently, there was extensive leptomeningeal spread of disease essentially caking the brain surface with a thick rind of tumor. Soon after, the boy succumbed to the disease.

Case 2 A 2-year-old Chinese boy presented to an outside facility with a 3-week history of fevers, sweating, vomiting and abdominal distention. The initial US and abdominal pelvic CT (CTDI 5.06 mGy) demonstrated a poorly defined, large hypodense heterogeneous mass centered in the right upper quadrant, involving most of the left lobe of the liver (Fig. 4). It extended posteriorly to invade the pancreatic head. This mass encased and displaced adjacent vessels. A separate small metastasis was seen in the right hepatic lobe. Additionally, there were bilateral lower lobe pulmonary nodules. In light of these findings, a working diagnosis of metastatic hepatoblastoma was made. Biopsy

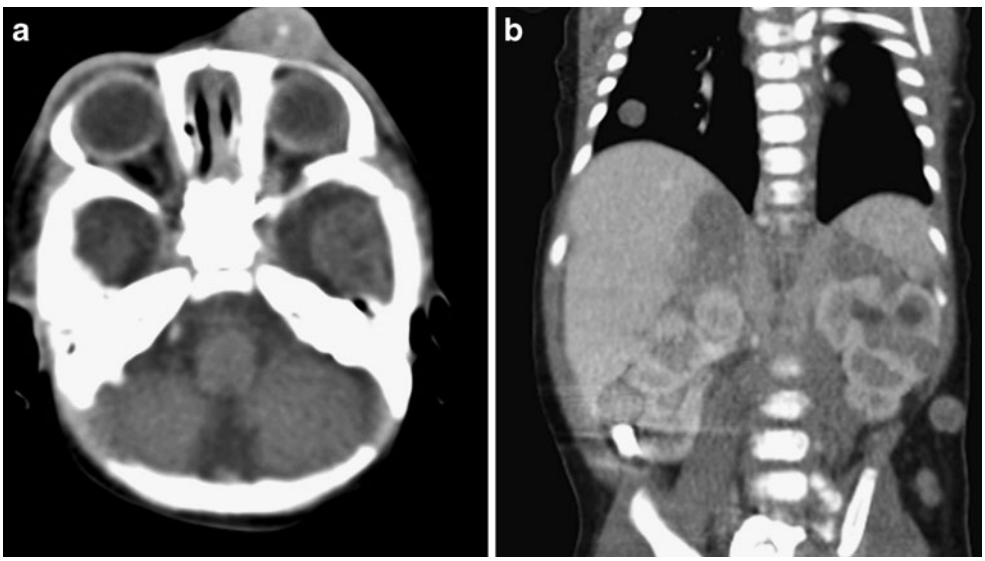

Fig. 1 CT images (case 1). **a** Initial noncontrast axial CT demonstrates a left-side partially calcified supraorbital mass. There is no bony involvement or intraorbital extension. **b** Coronal CT at presentation demonstrates a right lower lobe pulmonary nodule, bilateral suprarenal masses that extend into the retroperitoneum and bilateral renal masses, as well as subcutaneous masses in the left flank

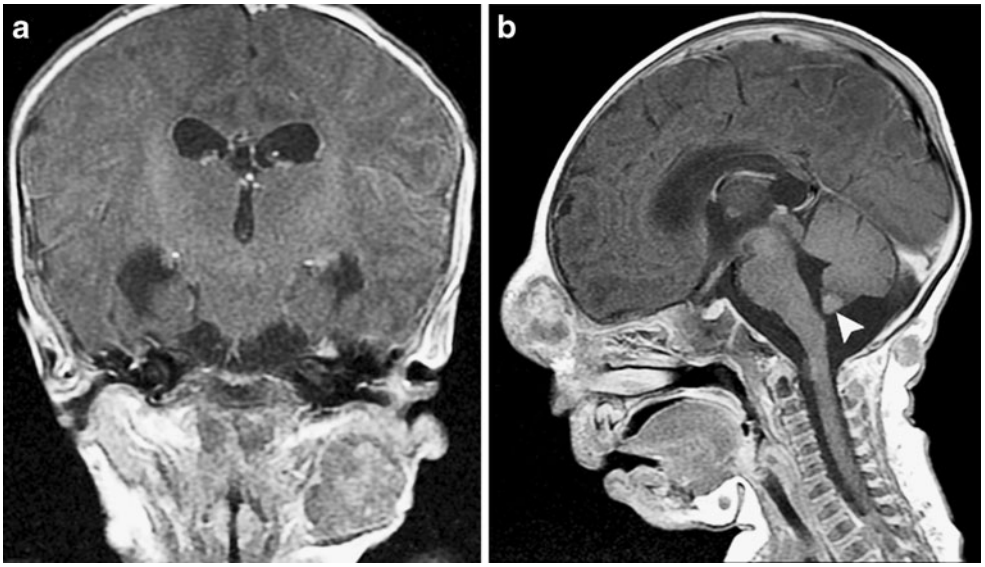

Fig. 2 MRI images (case 1). **a** Coronal postcontrast T1-weighted image demonstrates a heterogeneously enhancing left parotid metastatic lesion. **b** Sagittal postcontrast T1-weighted image demonstrates a homogeneously enhancing nodule in the cerebellar tonsil (*arrowhead*) as well as subcutaneous nodules, best seen within the soft tissues posteriorly Also pictured is the enlarging supra-orbital mass

of the hepatic mass was performed, and results confirmed an undifferentiated carcinoma showing the same karyotype appearance as noted in patient 1.

Chemotherapy was declined and there was continued progression of disease. Follow-up PET/CT scan demonstrated extensive FDG-avid omental caking from metastasis (Fig. 4), pulmonary nodules, mediastinal adenopathy and subcutaneous nodules. The primary tumor also had increased in size. There was significant progression of the pulmonary metastatic disease with large pleural effusions and subsequent death from respiratory failure.

Case 3 This is a remote case from 1996 that was resurrected for review following new awareness by our pathologists of the disease entity. Karyotyping of postmortem tumor tissue led to the confirmed diagnosis. This was a 14-year-old Caucasian girl who presented to an outside hospital with a solitary mass in the left thigh that was

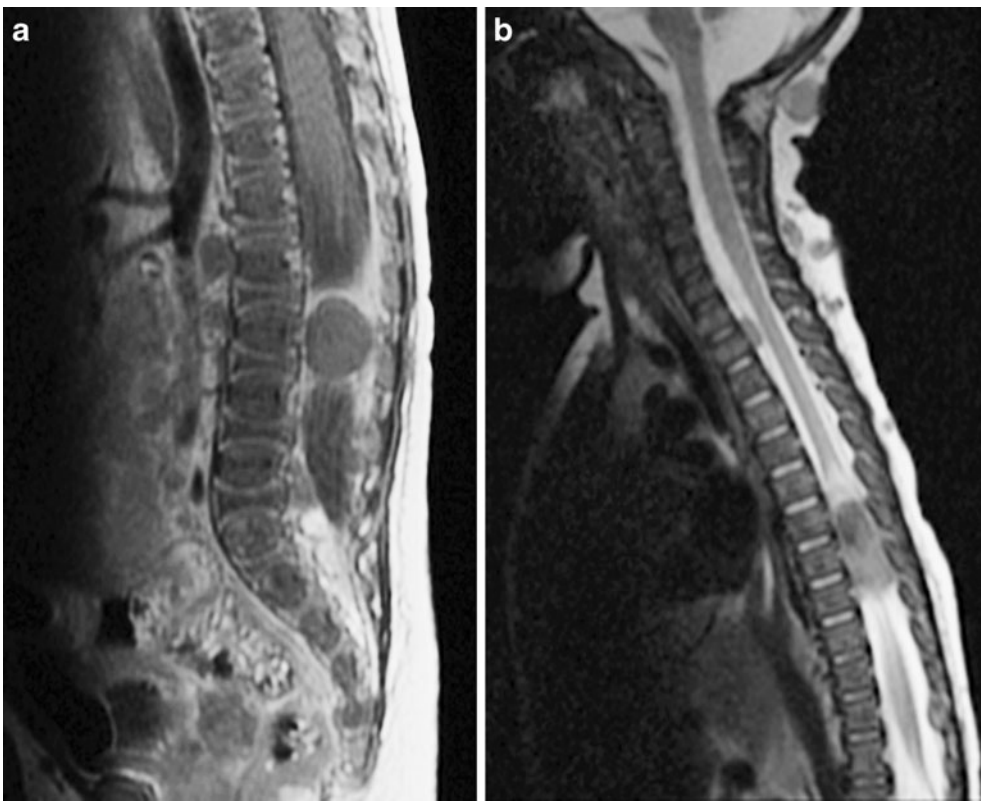

Fig. 3 MRI spine images (case 1) demonstrate intradural masses, as well as the subcutaneous masses. Lesions are (**a**) hypointense on T1-weighted and (**b**) heterogeneously low-level hyperintense on T2-W images

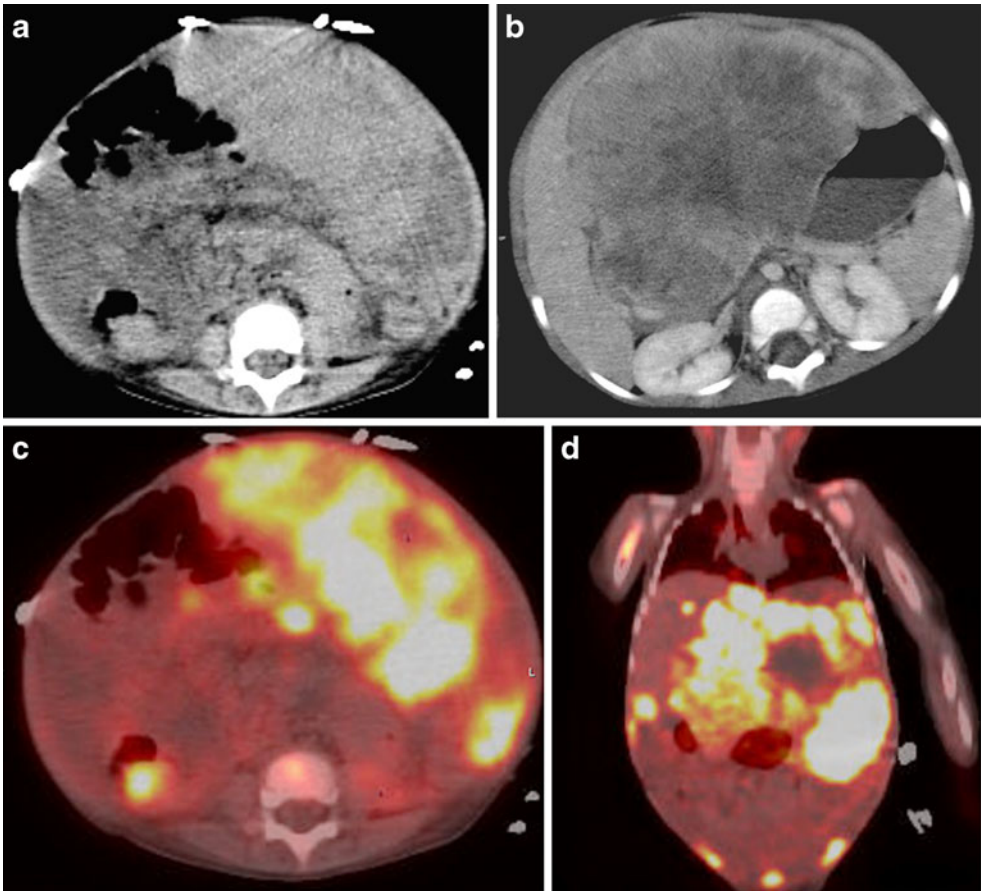

Fig. 4 CT and PET images (case 2). **a** Axial CT image shows **a** heterogeneous hypodense mass in the right upper quadrant involves most of the left hepatic lobe extending posteriorly to invade the pancreatic head. **b** Follow-up CT image demonstrates a large omental metastatic lesion mid-abdomen, extending to the left. Axial (**c**) and coronal (**d**) PET images demonstrate abnormal increased FDG uptake in primary hepatic and metastatic omental lesions

further evaluated with a contrast-enhanced MRI. The lesion was initially thought to represent a sarcoma. The MRI demonstrated a T1 hypointense heterogeneously enhancing mass that was T2 hyperintense (Fig. 5) in the medial

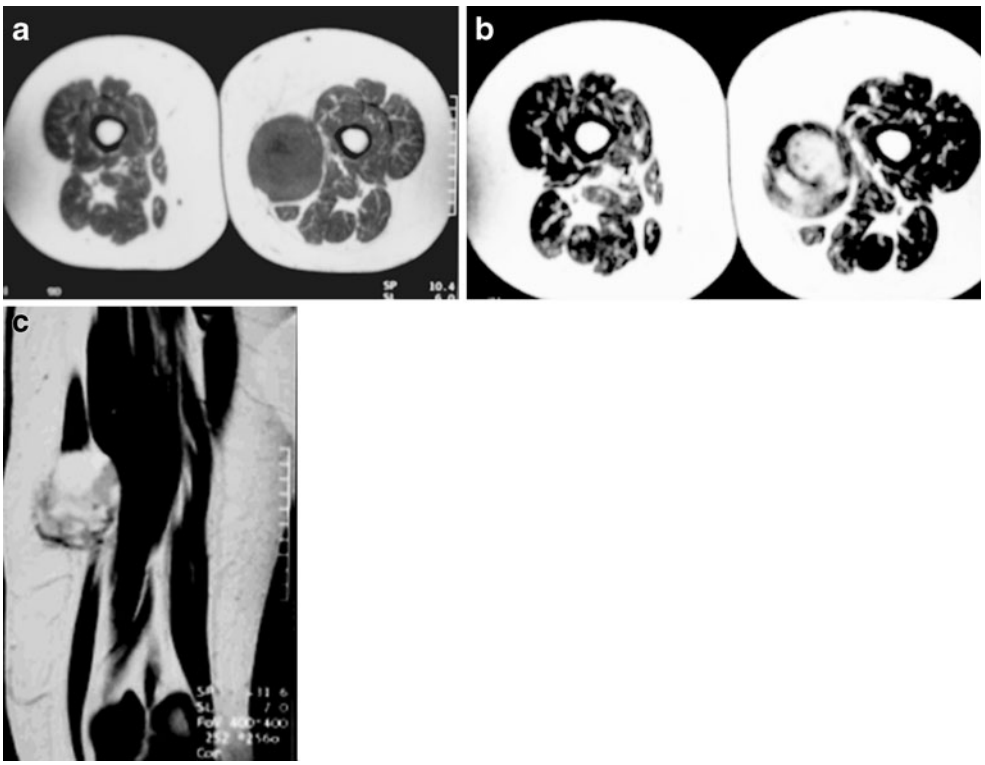

Fig. 5 MRI images of a left medial thigh mass (case 3). **a** Mass is hypointense on axial T1-W precontrast images. **b** Mass shows heterogeneous enhancement on axial T1-W non-fat-saturated post-contrast images. **c** The mass is hyperintense on coronal T2-W image without fat saturation

compartment of the left thigh. The tumor was resected and a diagnosis of rhabdomyosarcoma was rendered by an outside institution. She received chemotherapy with initial response; however, she relapsed after 11 months. She was transferred to our institution with shortness of breath for further care. Imaging at the time, according to the medical records, demonstrated extensive pulmonary metastatic disease with bilateral pleural effusions and the girl died from respiratory failure within days of admission. The images themselves were not available for review.

Discussion

The first published case of NUT midline carcinoma was reported in 1990 in Japan by Ichiro Kubonishi et al. [3]. The case was a 22-year-old woman with presumed thymic carcinoma that was refractory to chemotherapy and radiation [2, 3]. The diagnosis was made retrospectively by chromosome analysis using the standard Giemsa banding method [3]. In the United States, the first case was reported in a 12-year-old girl with an epiglottic mass [2]. This was diagnosed by fluorescence in situ hybridization (FISH) and the loci were finely mapped by southern blot [2]. The tumor is usually diagnosed by positive karyotyping for t(15;19) and confirmed with FISH.

Initially the tumor was called proline-rich undifferentiated carcinoma (PRUC) as the genetic makeup was high in proline [2]. The gene was initially thought to be expressed only in the testis and thus named NUT for nuclear protein in testis. Later, this gene was also found to be active in the ciliary body of the eye. According to the consensus nomenclature rules, NUT has been changed to C15orf55, but for simplicity the commonly used term is NUT [2]. Although this tumor is characterized by a rearrangement on the NUT gene, located on chromosome 15q14 [1–13], resulting in the BRD4-NUT fusion oncogene, this fusion is not always present, as was found by C.A. French et al. [2, 4] on retrospective studies of several undifferentiated carcinomas. French found that seven patients had the NUT gene, but only four had BRD4-NUT oncogene fusion; the other three only had the NUT chromosomal rearrangement and not the BRD4 and were termed the NUT variants [2, 4]. This variant is instead associated with the t(9;15), resulting in BRD3-NUT fusion oncogene [1]. However, after several iterations, the currently used name for this tumor is NUT midline carcinoma, as it is invariably associated with the NUT rearrangement [2] and the initially diagnosed tumors occurred in the midline, within the aerodigestive tract and the thymus [2, 5].

From the available literature, which is sparse, there has been no gender predilection. This lethal disease was thought to occur primarily in the pediatric and young adult population. However, the tumor has been reported in a patient as old as 78 years [1, 2]. There has been recent suggestion that the incidence of tumor being more common in the pediatric population could be a result of selection bias, with cytogenetic analysis performed more routinely in pediatric tumors [2, 4]. The average survival of patients with NUT midline carcinoma from initial presentation is poor, reported at 9–10 months in available literature [6, 7].

We present the imaging features of three children ages newborn, 2 years and 14 years with the diagnosis of NUT midline carcinoma. Pathology of two of our cases, the newborn and the 2-year-old, has been reported in the pathology literature; however, the imaging was not discussed in detail [4]. The clinical presentations varied in all three children. Symptoms were based on the location of the tumor in two of the three children. The other child presented with generalized symptoms of malaise and fever along with abdominal distension secondary to tumor location. Only one case report with CT imaging features has been described in the radiology literature [8].

In known cases to date, approximately 70% of patients present with midline tumors, most commonly in the head, neck and upper thorax [2, 5]. Interestingly, all three of the patients in this series had the bulk of the tumor below the diaphragm, although one presented with metastatic supraorbital mass. All three of the children had the classic chromosomal translocation, t(15;19) with BRD4-NUT oncogene expression. One child had the bulk of disease in the right suprarenal region extending across the midline to the left, the second child in the right upper quadrant, nearly completely involving the left lobe of the liver, and the third child in the medial compartment of the left thigh. There are two other cases of NUT midline carcinoma reported below the diaphragm, one in the bladder and the other in the right iliac wing [5, 9]. The more recent case of the right iliac wing tumor has the unique feature of successful treatment, with continuous remission close to 13 years since treatment [9]. At the time of presentation, metastatic disease is usually present, as in two of our three patients. Only one of our patients did not have metastatic disease at the time of presentation. Metastatic disease can involve almost any part or organ, according to our review of the literature. All of our patients had pulmonary nodules, and two of the three children succumbed to malignant pleural effusions resulting in respiratory failure. Subcutaneous nodules were present in two of our three patients. Subcutaneous and pulmonary metastatic nodules with NUT midline carcinomas have been reported [1, 10]. One of our three patients had intracranial and intraspinal involvement, which has been previously reported [8, 10]. One child had renal metastases and a metastatic lesion in the cul de sac and the other had a metastatic lesion in the omentum. Renal and adrenal

metastatic disease was considered rare. In a study by French et al. [4], only one of their 11 patients had renal metastasis and one had adrenal metastatic disease [4].

Imaging features are relatively nonspecific but consistent among patients. In two of our three patients who had CT scans at initial evaluation, the tumor demonstrated low density with heterogeneous enhancement; similar imaging features were described previously in the only case of a mediastinal mass in the radiology literature [8]. Intralesional necrosis was present in two of our three patients and was previously reported as well [5]. The tumor can encase and infiltrate adjacent structures. This finding was seen in both these patients, as well as previously described cases of mediastinal masses [7, 8]. Intralesional calcification was present in a metastatic lesion in one of our three patients, an entity not previously described in the literature to our knowledge.

MRI was performed in two of the children, with the tumor being heterogeneous but predominantly hypointense on T1-weighted images and hyperintense on T2 with heterogeneous postcontrast enhancement. Intracranial lesions demonstrated restricted diffusion in our one patient who had metastatic disease to the brain. One of our three patients had a PET/CT scan and the tumor was FDG avid, a finding that concurs with prior literature [7, 11, 12].

Diagnosis of this tumor by imaging is not likely, but including it in the broad differential diagnosis for tumors with atypical clinical presentation, course or radiologic findings that do not clearly fit into the more common tumors might lead to pathological diagnosis. Differential considerations usually depend on the site of the largest presenting tumor, the presumed site of origin. In our series of three children, the differential considerations included stage IVs neuroblastoma, hepatoblastoma and sarcomatous lesions, including rhabdomyosarcoma. Suspicion should increase if the tumor has an unfavorable response to the proposed primary working diagnosis. Last, presence of exponential interval growth should also be concerning for NUT midline carcinoma. It is important to be aware of this entity, especially when performing a biopsy to give ample viable tissue given the understandable challenges for the pathologist, as well [13].

Conclusion

This rare and typically lethal carcinoma usually presents in the midline, either in the head and neck or within the thorax. However, other cases presenting below the diaphragm have been described, including the cases described in this article, two of which had the bulk of the disease within the abdomen and one within the medial aspect of the lower extremity. The common imaging features include heterogeneous low density on CT, and T1 hypointensity and low-level T2 hyperintensity on MRI with heterogeneous enhancement. In patients who have undergone PET/CT, including one of our patients, the tumor is FDG-avid. Metastatic disease is common and can be extensive. The most striking feature of this disease is its aggressive and multifocal nature with exponential interval growth of tumor.

Ultimately, the purpose of publishing these data is to increase radiologists' awareness of this unusual and lethal disease.

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