CASE REPORT

Novel intronic *DICER1* variation associated with pleuropulmonary blastoma in two siblings

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SUMMARY

Pleuropulmonary blastomas (PPB) are rare aggressive paediatric lung malignancies associated with *DICER1* variants. We present two cases, a 2-year-old girl with upper respiratory tract symptoms as well as a 6-month-old girl sibling undergoing screening due to family history of malignancy. Imaging of the 2-year-old girl revealed a large mass filling the right hemithorax which was determined to be a type II PPB after pathological examination. Imaging of the 6-month-old sibling demonstrated a small cystic lesion in the posterior basal segment of the right lower lobe which was determined to be a type I PPB after pathological examination. The 2-year-old girl received adjuvant chemotherapy while the baby sister underwent resection alone and both are alive and well at 12 months and 7 months, respectively. Sequence analysis in both cases confirmed the same *DICER1* variation, c.2437-2A>G (likely pathogenic), which has not been previously described in the literature.

BACKGROUND

Paediatric malignancies comprise just 1% of all new cancer diagnoses in the USA per year. Of those, primary pulmonary malignancies are exceedingly rare, comprising only 0.2% of all paediatric malignancies.^{1,2} Those lung cancers seen in adults are seldom seen in children; however, they do occur. The most common primary paediatric lung malignancy is pleuropulmonary blastomas (PPB) (57.1%). However, paediatric lung malignancies are approximately 12 times more likely to represent a metastasis from another primary tumour.³ We describe two cases of PPB, one presenting with upper respiratory tract symptoms, and the other after precautionary screening, in siblings with a strong family history of malignancies associated with *DICER1* variants.

CASE PRESENTATION

A 2-year-old previously healthy girl presented with several months history of dry non-productive cough, and fatigue. Initially, the family consulted their paediatrician who recommended a humidifier and an antihistamine; no improvement in symptomatology was appreciated. During the several months course, she also developed rhinorrhoea and nasal congestion, but these symptoms resolved spontaneously. She then developed shortness of breath and became increasingly fatigued and irritable. These new symptoms were associated with a decrease in oral intake and urine output, which

prompted evaluation at an urgent care office. A chest X-ray was performed and revealed white-out of the entire right thorax with tracheal deviation to the left. She was immediately sent to the emergency department for further workup. In obtaining the family history, it was noted that the patient's cousin had been recently diagnosed with a pinealoblastoma and PPB which prompted familial genetic testing for *DICER1* variants. It was discovered that the patient's mother was a carrier, as was one of her brothers who is the father of the aforementioned cousin. Two of the mother's other siblings did not carry the variation, and two more did not know if they carried the variation, one of which has a child who was diagnosed with a medulloblastoma. The 2-year-old's maternal grandfather was also reported to have the variant, as well as an undefined thyroid problem, but he had not been diagnosed with any of the *DICER1* specific anomalies before passing away due to a stroke.

At approximately the same time, the 2-year-old's mother gave birth to a healthy baby girl. Due to the strong family history of malignancy in the setting of a known *DICER1* variation, she underwent genetic testing and radiographic screening to rule out early malignancy. The baby girl was asymptomatic at birth.

INVESTIGATIONS

During the 2-year-old's evaluation in the emergency department, an ultrasound (US) demonstrated a heterogeneous, echogenic mass filling the right chest with surrounding fluid and atelectatic lung. A follow-up CT chest with contrast was performed and showed a large, heterogeneous cystic and solid enhancing septate mass filling the entire right hemithorax from the apex to the base, with associated mass effect and leftward shift of the mediastinal structures (figure 1A). MRI of the brain did not reveal any evidence of intracranial metastasis. A CT abdomen/pelvis did not demonstrate evidence of intra-abdominal or intrathoracic metastasis or evidence of other disease processes of abdominal or pelvic organs. At this point a multidisciplinary discussion took place, and it was determined that surgery would be required. In addition to resection of the mass, a separate discrete subcentimetre nodule was found on the diaphragm at the time of surgery and was biopsied for suspected metastatic disease. Following resection, gross pathological examination of the 2-year-old's pulmonary mass revealed a 15.5×14×8 cm subpleural multicystic and solid mass varying in colour and consistency from white

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Figure 1 CT chest with contrast of (A) 2-year-old demonstrating a large heterogeneous cystic and solid septated mass occupying the right hemithorax with associated mass effect of the mediastinal structures; (B) 6-month-old sibling demonstrating a 7 mm cystic lesion (black arrow) in the posterior basal segment of the right lower lobe.

to dark brown and soft to firm. Within the cystic spaces were numerous grape-like nodular protrusions with similar characteristics. Histologically, the lung mass was composed predominantly of solid sheets of highly proliferative (mitotic count >10 mitoses per high powered field) blastemal-type cells with areas of necrosis. There was a predominance of rhabdomyosarcoma (figure 2A), as well as chondrosarcoma (figure 2B), and undifferentiated spindle cell sarcoma. Histopathological examination of the diaphragmatic nodule revealed similar findings.

Immunohistochemistry demonstrated positive immunoreactivity for myo-D1, myogenin and muscle-specific actin (figure 2C) in the tumour cells, and tumour cells lacked immunoreactivity for pancytokeratin, except in overlying normal respiratory epithelium. Electron microscopy was performed and showed immature appearing spindle cells with abundant intracytoplasmic glycogen with variable amounts of actin and myosin

Figure 2 (A) Area of rhabdomyosarcoma composed of rhabdomyoblasts containing eccentric eosinophilic granular cytoplasm (H&E, $\times 20$). (B) Area of chondrosarcoma composed of a cartilaginous matrix with malignant chondrocytes (H&E, $\times 20$). (C) Immunohistochemistry for muscle specific actin showing positive immunoreactivity in the area of rhabdomyosarcoma (Muscle specific actin (MSA), $\times 20$). (D) Electron microscopy showing spindle cells containing sarcomeres with prominent Z-bands (arrowhead) ($\times 2900$).

filaments as well as prominent sarcomere formation with distinct Z-bands (figure 2D). The gross and microscopic features in conjunction with radiographic imaging and the patient's family history led to classification as a type II PPB with metastasis to the diaphragm.

The 2-year-old's baby sister underwent genetic testing and was positive for a *DICER1* variation, and a screening chest X-ray 1 month after birth was unremarkable. Four months later, she underwent a chest CT which revealed a 6 $\times$ 7 mm cystic lesion with a single septum in the posterior basal segment of the right lower lobe (figure 1B). US examination of the abdomen and pelvis did not demonstrate evidence of intra-abdominal or intra-thoracic metastasis or evidence of other disease processes of abdominal or pelvic organs. Investigational imaging for other sites of metastasis were not undertaken as there have been no reported cases of type I or Ir metastasising.⁴ Due to the strong family history of malignancy and presence of the *DICER1* variation, it was felt that resection was reasonable given the potential for malignancy. At 6 months of age, she underwent resection of the cystic lung lesion. Gross examination demonstrated a 1.1 $\times$ 0.7 $\times$ 0.7 cm unilocular cystic lesion without solid areas. Histologically, the cyst was lined by benign appearing epithelium and lacked primitive or rhabdomyoblastic cell populations. This lesion was classified as type 1r PPB.

DIFFERENTIAL DIAGNOSIS

The differential for paediatric cystic lung disease includes a bronchogenic cyst, post-traumatic/postinfectious cyst, congenital pulmonary airway malformation (CPAM) and cystic forms of PPB. On radiographic grounds, cystic PPBs (type I) may be indistinguishable from CPAM, namely CPAM type 4.⁵ If one considers the diagnosis of PPB, the differential also includes primary sarcomas of the lung, including rhabdomyosarcoma, fibrosarcoma and chondrosarcoma. Solid areas within PPBs may show various degrees of mesenchymal differentiation, and as PPB is the most common malignant paediatric tumour primary to the lung it should be considered first.⁶ PPB should not be confused

with pulmonary blastoma, a tumour seen more commonly in adults that is characteristically biphasic.^{3,6}

CPAM, previously called congenital cystic adenomatoid malformation, accounts for up to 95% of congenital cystic lung disease.⁷ CPAMs are classified as types I–IV based on cyst size and multiplicity, the lining epithelium of the cyst and the proportion of the lung involved.⁸ CPAM type IV, accounting for approximately 10%–15% of CPAMs, may resemble type I PPBs.^{8,9} Careful histological examination for the presence of immature/primitive mesenchymal cells is necessary for separating CPAM from PPB. This may be even more challenging in cases of ‘regressed’ type I PPBs. The presence of increased stromal cellularity within cyst walls should raise suspicion for a PPB when there is cystic lung disease that clinically appears to represent a CPAM.⁹ It is essential to exclude type I PPB before a lesion is classified as CPAM type IV.^{10,11}

Primary sarcomas of the lung in the paediatric population are uncommon, some of which may be misdiagnosed and are actually a component of a PPB.¹² Cystic synovial sarcoma, though usually seen in older patients, may also be considered.⁵ In such cases, immunohistochemistry and molecular studies show the characteristic translocation, t(x;18)(p11.2;q11.2), resulting in a gene fusion (SYT-SSX1 or SYT-SSX2), which can be assessed using break-apart fluorescence in situ hybridization (FISH) analysis.^{13–16}

TREATMENT

The 2-year-old underwent a right middle lobectomy with complete removal (negative surgical margins) of the type II PPB and biopsy of the PPB in the diaphragm. She then received 36 weeks of adjuvant chemotherapy according to the International Pleuropulmonary Blastoma Registry, which includes vincristine, actinomycin D, doxorubicin and ifosfamide. Radiation therapy was not considered given the complete removal of the main lesion and unknown utility of its use in these tumours.

The 6-month-old sibling underwent a right lower lobectomy with complete removal (negative surgical margins) of the type Ir PPB. Due to early detection and resection, she is being followed conservatively without chemotherapy.

OUTCOME AND FOLLOW-UP

The 2-year-old girl was diagnosed with type II PPB and biopsy proven metastasis to the diaphragm with no other known sites of involvement. Genetic testing of *DICER1* demonstrated a familial, likely pathogenic (based on American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) criteria) heterozygous germline *DICER1* variant, c.2437-2A>G (Splice acceptor) and a heterozygous germline variant of uncertain significance, c.4199A>G (p.Asp1400Gly). She completed 36 weeks of adjuvant chemotherapy. Three months after the completion of chemotherapy, and 12 months post diagnosis, she is clinically well and remains in remission. Follow-up imaging to monitor for recurrent pulmonary disease will include chest CT’s looking for recurrence, MRI for brain metastasis, early US of the ovaries and thyroid.

As mentioned previously, the 6-month-old carries the same heterozygous germline variation found in her older sister. She is currently 7 months post surgical resection and is clinically doing well. No additional PPB lesions have developed. Follow-up imaging to monitor for recurrent pulmonary disease will include chest CT’s and early US of the ovaries and thyroid.

DISCUSSION

PPB were first described as distinct pulmonary malignancies of childhood with mesenchymal differentiation by Manivel *et al* in 1988. This was in comparison with pulmonary blastomas of adulthood which contain both epithelial and mesenchymal differentiation.^{17,18}

PPBs can be separated into three distinct subtypes based on gross and microscopic differences. Type I PPBs are cystic. Cysts are lined by benign-appearing epithelium and have an underlying hypercellular region of immature appearing malignant mesenchymal cells forming the so-called ‘cambium-like layer’. A subtype of type I PPBs, type Ir (regressed), lack the typical underlying region of immature malignant cells. Type II PPBs are cystic and solid, with cystic areas resembling type I PPB and more solid areas composed of sarcomatous components which may include rhabdomyosarcoma and/or chondrosarcoma among others. Type III PPBs are solid, resembling the solid areas of type II tumours and lacking the cystic areas of type I tumours. It is widely accepted that these types occur on a developmental spectrum, beginning as a type I and progressing to type II or III.^{4,19,20} The median age at the time of diagnosis for types I, II and III are 8, 35 and 41 months, respectively.⁴

PPBs have recently been determined to be a part of a familial cancer syndrome due to variants in the gene *DICER1*.²¹ In addition to PPBs, individuals with *DICER1* variants are at risk for other malignant and non-malignant lesions of the thyroid, nose and sinuses, pituitary, kidney, ovary, uterus, eye and others.²² *DICER1* encodes an endoribonuclease (RNase III) critical in the production of micro-RNA (miRNA). Sequencing of *DICER1*-associated tumours has demonstrated biallelic variants in *DICER1*. It has been shown that one allele typically contains a nonsense or frameshift variant leading to complete loss of function (usually germline), while the other allele contains a missense variant (usually somatic) in one of five so-called hotspot codons (E1705, D1709, G1809, D1810 and E1813) in the RNase IIIb domain. Variants leading to complete loss of function do so by truncating the open reading frame before the end of the RNase IIIb domain, while variants in one of the hotspot codons leads to defects in miRNA processing. In particular, cleavage of 5p miRNAs at the 5’ end fails while cleavage of 3p miRNA at the 3’ end is preserved. This leads to an inverse of the 5p to 3p mature RNA ratio observed in otherwise normal tissue, which suggests that uncleaved 5p miRNA is rapidly degraded. Loss of 5p miRNA leads to altered expression of downstream tumour suppressor mRNAs, such as the *let-7* family, and may lead to uncontrolled proliferation. The majority of individuals with *DICER1*-associated tumours harbour a heterozygous germline loss of function variant as the predisposing variant. However, a small percentage of individuals who lack detectable pathogenic germline variation in *DICER1* (assuming *DICER1* deletion has been ruled out) harbour low-level *DICER1* mosaicism or tumor-confined pathogenic *DICER1* variation.²³ It appears that biallelic disruption of *DICER1* is necessary for tumorigenesis and is a variant on Knudson’s two-hit hypothesis. Of note, no cases with biallelic loss of function variants have been reported, leading to the hypothesis that at least some functional activity is necessary for tumour survival.^{4,23,24}

The specific *DICER1* variation reported herein as likely pathogenic, c.2437-2A>G (NM_177438.2), has not been previously reported in the literature. According to Invitae, this variant results in a sequence change in intron 15 of *DICER1*. Algorithms to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site

resulting in an absent or disrupted protein product. However, published transcriptional studies have not been done to confirm this. It is known that donor and acceptor splice site variants lead to a perturbation in protein function, and that loss of function variants in *DICER1* are pathogenic.^{21 25 26} In addition, reports of intronic *DICER1* variants have been reported in association with PPB, although rarely, and there is a recent report by Schultz *et al* of a novel intronic *DICER1* variant associated with Sertoli-Leydig cell tumour.²⁷ These observations, although yet to be proven, are evident enough that this variant is likely pathogenic. In addition, the variant of uncertain significance, c.4199A>G (p.Asp1400Gly) (NM_177438.2), has been reported in the literature, but it has not been associated with *DICER1*-associated phenotypic features. According to Invitae, this variant leads to a missense variation with glycine replacing aspartic acid at codon 1400 of *DICER1*. Algorithms developed to predict the effect of such a variation suggest that this variant is likely to be tolerated. However, published functional studies have not been done to confirm this. In this case, the tumour was not tested for hotspot variants, as the family declined additional genetic testing.

Treatment for PPBs is largely based on the International Pleuropulmonary Blastoma Registry group (IPPB) recommendations. It is their recommendation that all type I PPBs be removed due to their progression over time to types II and III, followed by chemotherapy with vincristine, actinomycin D, cyclophosphamide. Similarly, it is the recommendation of the IPPB that type Ir PPBs receive chemotherapy similar to type I PPBs, although this is not accepted by many. Five-year overall survival for patients with types I and Ir is 91%.⁴ Type II and III lesions are treated as one group and their recommendation, based on unpublished observations, is initial surgical resection if feasible followed by chemotherapy with vincristine, actinomycin D, ifosfamide and doxorubicin. If the tumour is too large for initial resection, neoadjuvant chemotherapy followed by surgery is recommended. The utility of radiation therapy is not well studied but is recommended in cases of residual tumour after surgical and failed chemotherapeutic attempts. The 5-year survival for type II and III PPBs is 71% and 53%, respectively.⁴

According to Schultz *et al*, those individuals with a diagnosis of PPB of any type, as well as any of a number of major or minor indications in addition to family history of *DICER1*-associated conditions, should undergo genetic screening for *DICER1* variants. If an individual desires not to pursue genetic testing, it is recommended that they follow surveillance guidelines as if they had a *DICER1* variant until genetic testing proves otherwise. If an individual with any of the indications proposed by Schultz *et al* undergoes genetic screening but does not have a germline *DICER1* variant, it is recommended that additional genetic testing for duplications/deletions be done as copy number variants are responsible for some cases. In those individuals who have a tumour that meets the indications for *DICER1* testing, whether a germline variant is present or not, tumour tissue should be tested to identify somatic variants. If only somatic variants are identified, this suggests a non-inherited case and screening of first-degree relatives is not recommended. However, if a germline variant is identified, screening of first-degree relatives is recommended. Whether there is a positive family history or a personal history of *DICER1*-associated conditions, screening of other organs is recommended for early detection of lesions. Prenatal screening is recommended in the third trimester with a US for the detection of pulmonary cysts. If a cyst is identified, follow-up with postnatal CT is required. Postnatal screening needs to take into consideration the median age of onset of these conditions, the organ systems at risk and the benefit of early

detection to the risks associated with the screening methodology. It is recommended for surveillance of the lungs that a chest X-ray be obtained every 4–6 months until 8 years of age, with consideration of a chest CT at 3–6 months, and a yearly chest X-ray thereafter until age 12; for female patients, starting at ages 8–10, that pelvic and abdominal USs be obtained every 6–12 months until at least age 40; for the kidneys, an abdominal US be obtained every 6 months until age 8 with yearly USs obtained thereafter until age 12; and for thyroid a baseline US by age 8 with an additional US every 3 years thereafter unless symptoms emerge. For full screening recommendations, refer to 28²⁸

In support of these screening recommendations, the finding of PPB in the older sibling lead to judicious use of imaging of the baby sister which lead to the early detection of the type Ir PPB and potentially improving her outcome significantly.

Learning points

- ▶ Pleuropulmonary blastomas (PPB) are distinct malignancies of childhood associated with *DICER1* variants.
- ▶ There are three different types of PPB, types I–III, based on morphology.
- ▶ The family history of malignancy, especially *DICER1*-associated tumours, prompted genetic testing and the successful diagnosis of a child with otherwise non-specific respiratory symptoms.
- ▶ Following *DICER1* genetic testing, surveillance for *DICER1*-associated tumours, as per published guidelines, was conducted on the younger sibling and resulted in the successful detection and resection of an early-stage PPB.

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