Clinical and molecular features of pleuropulmonary blastoma in children in Hong Kong: case reports

Anthony PY Liu[1], MB, BS, **Marcus KL Fung**[1], PhD, **Mianne Lee**[1], MSc, **Jasmine LF Fung**[1], BSc, **Mandy HY Tsang**[1], MMedSc, **CW Luk**[2], MB, BS, **Brian HY Chung**[1], MB, BS, MD, **Godfrey CF Chan**[1]*, MD

[1] *Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong*
[2] *Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong*

* Corresponding author: gcfchan@hku.hk

Hong Kong Med J 2022;28:328–30
https://doi.org/10.12809/hkmj219503

Case reports

Patient 1

In January 1998, a 14-month-old girl presented with fever and dyspnoea. Plain chest radiograph showed opacification of the right hemithorax that corresponded to a multicystic mass on computed tomography. Thoracotomy was performed and a 11-cm × 9.5-cm × 5-cm mixed cystic-solid mass excised. Together with histological findings, type II pleuropulmonary blastoma (PPB) was diagnosed. The patient was treated with adjuvant chemotherapy according to the Intergroup Rhabdomyosarcoma Study-IV regimen but developed ifosfamide-induced renal tubulopathy. At the time of writing, the patient remains in remission (age 23 years). Sanger sequencing revealed no *DICER1* mutation in the patient's peripheral blood DNA.

Patient 2

In November 2008, a 9-month-old girl presented with progressive dyspnoea. Plain chest radiograph revealed left-sided pneumothorax. Computed tomography scan of the thorax after thoracocentesis revealed a 3-cm cystic lesion in the lingula, suspicious of congenital cystic adenomatoid malformation. In view of the risk of recurrent pneumothorax, left upper lobectomy was performed. Microscopically, features of the excised lesion were compatible with type I PPB. No adjuvant treatment was required and the patient remained in remission for 10 years. Multinodular goitre (MNG) was also diagnosed at age 7 years. Sanger sequencing of the patient's peripheral blood DNA revealed a heterozygous frameshift mutation in *DICER1* (NM_177438.2:c.4022del(p.(Gly1341Alafs*6)); Fig 1), inherited from her father (Fig 2), who also had a history of MNG with thyroidectomy done. Familial counselling was offered with discussion about the role of further cascade testing and recommendations for surveillance.

Patient 3

In December 1999, a 2-year-old girl presented with presumed right-sided pneumonia unresolved for 2 months. Computed tomography scan of the thorax

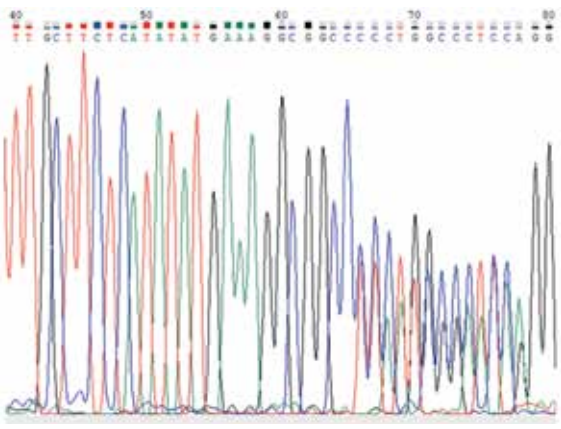

FIG 1. Sanger sequencing indicating germline *DICER1* mutation in the proband of Case 2

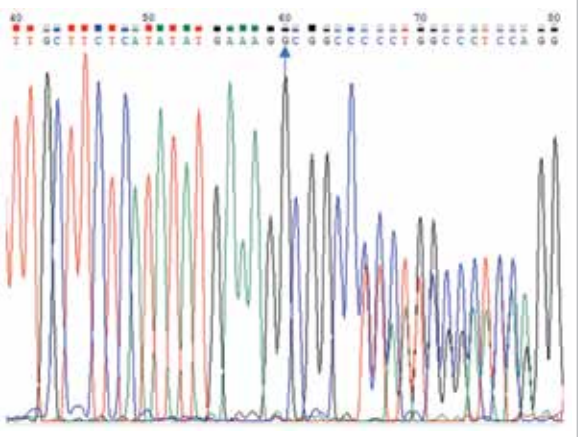

FIG 2. Sanger sequencing indicating germline *DICER1* mutation in the father of Case 2

showed collapse-consolidation with pleural effusion. Exploratory thoracotomy revealed a huge mass in the right middle lobe and debulking was performed. Histology confirmed type II PPB. A new computed tomography scan of the thorax demonstrated a residual multiloculated cystic mass with intermixed solid components. Adjuvant chemotherapy based on the Intergroup Rhabdomyosarcoma Study-IV regimen was adopted. Right middle lobectomy was performed after week 8 of chemotherapy. The patient subsequently developed cerebral relapses at age 7 years and again at age 17 years for which she was treated with excision and chemoradiotherapy (ifosfamide/carboplatin/etoposide + 40-Gy focal radiotherapy and irinotecan/temozolomide + 40-Gy focal radiotherapy, respectively). At the time of writing, the patient (age 21 years) has been in remission for 4 years. Multinodular goitre was also diagnosed at age 13 years. A heterozygous frameshift mutation in *DICER1* was detected in the patient's peripheral blood using Sanger sequencing (NM_177438.2:c.1651_1654delGGAA(p(Gly551Glufs*10)); Fig 3).

Patient 4

In January 2016, a 2-year-old girl presented with fever, cough and progressive dyspnoea. Computed tomography of the thorax revealed a large space-occupying lesion in the right thoracic cavity, with pleural effusion, mediastinal shift and superior vena cava compression. Biopsy confirmed type III PPB. Considering the risk of upfront surgery, neoadjuvant chemotherapy with ifosfamide, vincristine, actinomycin and doxorubicin was started. Unfortunately her response was suboptimal and she developed respiratory embarrassment and required emergency surgery during which she went into cardiopulmonary arrest. Despite successful resuscitation and debulking surgery, the patient demonstrated signs of severe hypoxic ischaemic encephalopathy. In view of the poor neurodevelopmental prognosis, the family elected to continue only palliative care. The patient eventually succumbed to progression 6 months after diagnosis. Sanger sequencing of peripheral blood DNA showed a nonsense mutation on exon 7 of *DICER1* (NM_177438.2:c.1174C>T, p.R392*; Fig 4); her father tested negative for the same germline mutation and her mother was not available for evaluation.

Discussion

Pleuropulmonary blastoma is a rare thoracic tumour that arises during infancy or young childhood.[1] Its aggressiveness and presenting features vary according to the histological subtype, ranging from the self-limiting cystic form (type I) with potential to undergo spontaneous regression (type Ir) or

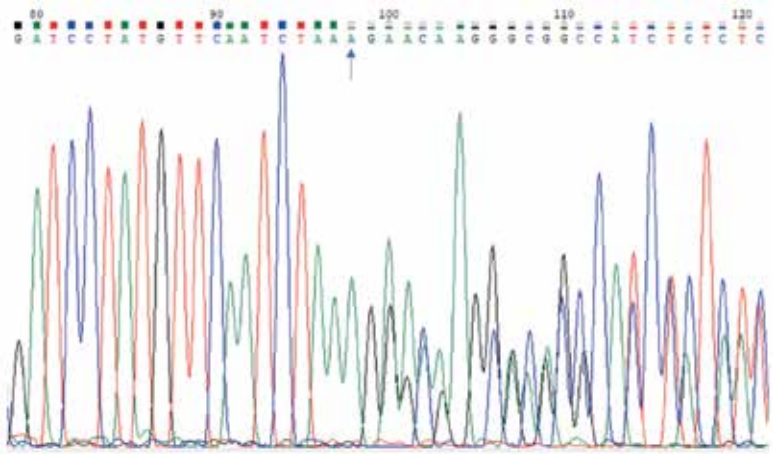

FIG 3. Sanger sequencing indicating germline *DICER1* mutation in proband of Case 3

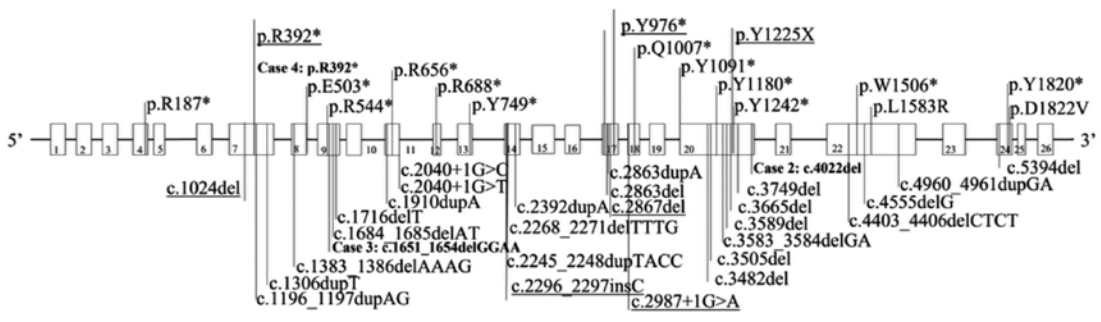

FIG 4. Germline *DICER1* mutation spectrum on genomic DNA of patients with pleuropulmonary blastoma with reference data from the Human Gene Mutation Database (https://www.hgmd.cf.ac.uk/), a recent report on Chinese patients with pleuropulmonary blastoma[4] (underlined text) and our results of Cases 2, 3, and 4 (bold text). NM_177438.2 was used as the reference sequence for DNA bases. The amino acid numbering used begins with the Kozak consensus sequence. *: stop codon

the mixed cystic/solid form (type II) that would benefit from adjuvant cytotoxic treatment, to a solid form (type III) that carries a considerable risk of disease relapse despite multimodal therapy. As an entity originally designated in 1988, familial clustering of PPB was first reported in 1996. This led to the recognition of underlying germline *DICER1* alterations, and subsequently the definition of *DICER1* syndrome—an autosomal dominant condition with variable penetrance and associated with almost 30 neoplastic conditions, including MNG, cystic nephroma, and ovarian stromal tumours.[2] The oncogenic mechanism consequent to *DICER1* mutations is hypothesised to be related to the resulting imbalance of mature miRNAs derived from the 5′ and 3′ ends of the precursor pre-miRNA. Because of its rarity, data on the presentation and molecular features of patients with PPB in Chinese are limited and that in Hong Kong have never been reported.

We reviewed a territory-wide paediatric oncology database and report the various presenting features and clinical course of four patients with PPB treated between 1998 and 2020. Type I/type Ir PPB should be considered in cases of cystic lung lesions; while many represent as incidental findings, the risk of pneumothorax remains a concern for peripherally located lesions. Among those where resection has been performed, 90% will remain progression-free without the use of adjuvant chemotherapy.[1] Type II and III PPB are differential diagnoses for young children (age <6 years) who present with a space-occupying thoracic mass or apparent, persistent chest infection. The surgical and perioperative management of massive lung lesions with mediastinal compression carries a high-risk of cardiovascular compromise and necessitates care at a tertiary referral centre with available expertise including extracorporeal membrane oxygenation support. For adjuvant therapy, the addition of doxorubicin to ifosfamide, vincristine and actinomycin has been shown to be efficacious in Types II/III PPB.[3] However, half of these patients still develop progression by age 5 years, 60% with a central nervous system component.

The prevalence of germline pathogenic *DICER1* mutations in the general population is estimated to be 1:10 600 in the ExAC-nonTCGA (The Cancer Genome Atlas) database, although mutations have been identified in two-thirds of patients with PPB with thus far a lack of genotype-phenotype correlation. In our series, novel heterozygous germline *DICER1* frameshift mutations were found in cases 2 and 3; while a heterozygous germline nonsense mutation, reported recently in another Chinese patient, was detected in Case 4 (Fig 4).[4] The findings of our case series add to the spectrum of known *DICER1* mutations, especially to the very limited data from Asia.[4] Diagnosing *DICER1* syndrome facilitates surveillance of associated morbidities, familial testing and reproductive counselling for both probands and symptomatic carriers.[5] Further studies and consideration of a prospective patient registry to define the prevalence of *DICER1*-associated conditions in both paediatric and adult populations in Hong Kong are warranted.

Author contributions

Concept or design: APY Liu, MKL Fung, BHY Chung, GCF Chan.
Acquisition of data: All authors.
Analysis or interpretation of data: APY Liu, MKL Fung, M Lee, JLF Fung.
Drafting of the manuscript: APY Liu, MKL Fung.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Acknowledgement

We would like to thank the patients and family for their consent to this study.

Funding/support

This study was supported by The Society for the Relief of Disabled Children. The funder had no role in study design, data collection/analysis/interpretation or manuscript preparation.

Ethics approval

This study was approved by the Institutional Review Board of the University of Hong Kong (Ref No. UW12-211) with informed consent obtained from patient guardians.

References

1. Messinger YH, Stewart DR, Priest JR, et al. Pleuropulmonary blastoma: a report on 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry. Cancer 2015;121:276-85.
2. de Kock L, Wu MK, Foulkes WD. Ten years of *DICER1* mutations: provenance, distribution, and associated phenotypes. Hum Mutat 2019;40:1939-53.
3. Doros LA, Schultz KA, Harris A, et al. IVADo treatment of type II and type III pleuropulmonary blastoma (PPB): a report from the International PPB Registry. J Clin Oncol 2014;32(15 Suppl):10060.
4. Cai S, Wang X, Zhao W, Fu L, Ma X, Peng X. *DICER1* mutations in twelve Chinese patients with pleuropulmonary blastoma. Sci China Life Sci 2017;60:714-20.
5. Schultz KA, Williams GM, Kamihara J, et al. *DICER1* and associated conditions: identification of at-risk individuals and recommended surveillance strategies. Clin Cancer Res 2018;24:2251-61.