The Imaging Findings of DICER 1 Syndrome - A Pictorial Review

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Learning objectives

- Increase awareness of DICER1 syndrome among radiologists.
- Provide a synopsis of the genetics and clinical manifestations of the DICER1 mutation.
- Familiarise radiologists with the salient imaging feature of DICER1 syndrome.
- Highlight the significance of 'incidental lesions’ seen on staging imaging in the setting of a detected primary that may point to the presence of DICER1 syndrome.
**Background**

DICER1 syndrome is a rare inherited disorder, due to an underlying mutation of the DICER1 gene, which increases the risk of developing several benign and malignant lesions, predominately manifesting in childhood. The most common organs affected are the lungs, kidneys, as well as several of the endocrine organs; thyroid, pituitary and ovary. [1-2]

The DICER1 gene is located on the long arm of chromosome 14 at position 32.13 (14q32.13), and encodes an RNase endonuclease. [3] The DICER1 protein (ribonuclease III) processes pre-microRNAs to functioning microRNAs. MicroRNAs are thought to be essential to the expression of over 30% of protein coding genes [4]. DICER1 is thus integral for production and regulation of further gene expression, protein synthesis, cell growth, division, differentiation and maturation. [1,4]

The link between the DICER1 gene and pleuropulmonary blastoma (PPB) was described in 2009 by Hill et al [5]. The mechanism of tumour predisposition is believed to operate by a haploinsufficiency mechanism, differing from the majority of described cancer predisposition genes. [4,5] The exact mechanism of oncogenesis is not yet fully understood. The majority of DICER1 mutation carriers are phenotypically normal throughout their lives. [4,6]
Findings and procedure details

Pleuropulmonary blastoma

Although relatively rare, with between only 25 to 50 children diagnosed with PPB in the United States each year, PPB remains the most common primary lung malignancy of childhood. [6-7] It is characterised histologically by a primitive mix of blastematosous and sarcomatous cells and can be regarded as a dysontogenetic analogue to Wilms tumour, neuroblastoma and hepatoblastoma. [8-9] PPBs are the most commonly associated tumour to the DICER1 syndrome. Furthermore, PPB leads the highest overall mortality of any of the associated tumours. [6]

PPBs are sub-classified into 3 clinico-radiological-pathological subgroups [8,10,11]

- Type I - Cystic: Multiloculated with thin septa. Often indistinguishable from CPAM on imaging [9] See figure 1.
- Type II - Cystic and solid - air filled cysts with variable solid component
- Type III - Solid - heterogeneous, enhancing mass

Type I considered benign, type II and III considered to be malignant [1]. PPBs most commonly metastasize to the CNS, bone and liver. [13] Depending of the morphology, differential diagnosis on imaging includes congenital pulmonary airways malformations (CPAM), congenital diaphragmatic hernia, bronchopulmonary dysplasia, sarcomas (solid) and congenital lobar emphysema.

Renal Tumours - Cystic Nephroma and Nephroblastoma (Wilms tumour)

Cystic nephroma is a rare benign cystic tumour of the kidneys. Tumours are usually unilateral and present in the first 2 years of life. [12] Most Wilms tumours are sporadic, though at least 5% of Wilms tumours are familial, with numerous associated syndromes including WAGR, Beckwith-Wiedermann, Denys-Drash and Perlman syndromes. [13] This is the most reported associated tumour with PPB in DICER1 syndrome. [4] Imaging typically demonstrates a well defined multi-loculated cystic intra-renal mass with thin internal septa and thick fibrous capsule without solid nodules (figure 2). Fine vessels may be seen within the septa. [11]

Nephroblastoma, also eponymously known as Wilms tumour is an embryonal cancer of the kidney and the most common intra-abdominal malignancy of childhood. [4,14,16] Histopathologically, cystic nephroma and Wilms tumours are similar, and it is postulated that they represent two ends along the spectrum of the same entity. [9] Several instances
have been described of Wilms occurring in patients with underlying DICER1 mutations, though this only accounts for a fraction of overall Wilms cases (figure 3).

**Multi-nodular Thyroid**

Thyroid disease is the most common endocrine organ involved with DICER1 syndrome. [2] Thyroid disease associated with DICER1 most commonly manifests as multinodular goitre (figure 4), with differentiate thyroid carcinoma less common. [2] Enlargement of the thyroid (goitre) due to nodular thyroid hyperplasia is the most common manifestation of thyroid disease, [2,14] and thus only a tiny fraction of those with thyroid lesions are associated with the DICER1 mutations.

**Ovarian sex-cord stromal tumours**

The ovarian stroma develops from undifferentiated gonadal mesenchyme of the sex cords of the embryonic gonad. In females this normally differentiates into the granulosa and thecal components of the ovary. The potential for tumourigenesis from the undifferentiated precursor allows a spectrum of tumours to arise. [14] Ovarian Sertoli-Leydig (androblastoma) tumours exhibit testicular differentiation and account for 8% of all ovarian tumours. [15]

On imaging tumours are usually unilateral, solid heterogeneous lesions, demonstrating internal vascularity on ultrasound. [16]

In DICER1 syndrome ovarian sex cord tumours are amongst the more frequent manifestations, in particular Sertoli-Leydig cell tumours. [2,15] Compared to sporadic cases, those with DICER1 associated sex cord stromal tumours present at a younger age. [6] Juvenile granulosa cell tumor and gynandroblastoma have also been associated. [6] There is some evidence to suggest a possible associated between ovarian germ cell tumours, with case reports of this, though a causal relationship has not been established. [15] A link has not been established between the DICER1 mutation and testicular tumours. [17]

**Pituitary blastoma**

Pituitary blastoma is a very rare aggressive pituitary tumour, described only in 2008, with only 12 pathologically confirmed cases described. [2,18,19] Pituitary blastoma presents before the age of 24 months, with endocrinopathy related to elevated adrenocorticotropic hormone (ACTH), and / or ocular symptoms related to local mass
effect. [2] Genetic assessment suggests this is highly associated with DICER1 mutations. [2,18]

Other rare tumours

Nasal chondomesenchymal hamartoma, ciliary body medulloepithelioma, rhabdomyosarcoma of the uterine cervix (sarcoma botryoides), intestinal hamartomatous polyps and ocular medulloepithelioma have also been described with DICER1 syndrome. [2, 4, 6, 15]
Fig. 1: CT images of Pleuropulmonary Blastoma in a patient with DICER1 syndrome - Scout image and axial CT slices through the chest with lung algorithm show a multiloculated cystic lesion centred on the right upper lobe, with thin septa and positive mass effect on the mediastinum. Removal and pathological assessment confirmed the presence of a type I PPB.

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Fig. 2: Multicystic nephroma in a patient with DICER1 syndrome - Top row comprises B-mode and colour Doppler images of a left renal mass. This is multi-loculated with thin septa, low level septal colour flow. The bottom row comprises non enhanced axial CT (left), and contrast enhanced axial CT images (middle and right). The first 2 are at the same level and show mild peripheral and septal enhancement. The right image shows a classic 'claw sign'.

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Fig. 3: Wilms tumour in a patient with DICER1 syndrome - Top row; B-mode and colour Doppler images show a solid mass with internal vascularity arising from the right kidney and abutting the liver. Bottom row; pre and post contrast axial CT images demonstrate an enhancing tumour arising from the right kidney (also demonstrating the 'claw sign')

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**Fig. 4:** B-mode and colour Doppler images (top row), and unenhanced axial CT images with coronal reformats (bottom row), show thyroid nodules in both lobes of the thyroid in a patient with DICER1 syndrome. Typical findings of a multinodular goitre is a heterogeneously enlarged thyroid gland with multiple non-calcified well circumscribed isoechoic nodules and hypoechoic cystic spaces dispersed on a heterogenous background parenchyma.

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Conclusion

DICER1 syndrome has only recently been described, and to date the limited, but increasing, amount of literature is predominately in genetics and other medical journals. There is a paucity of material within the radiological literature.

Imaging can play an integral role in identifying an underlying diagnosis of DICER1 syndrome. When encountering a tumour such as a Wilms or cystic nephroma, incidental note of lesions in the lungs, pelvis and thyroid, either on the initial or follow up imaging should prompt consideration of DICER1 syndrome. The diagnosis of DICER1 should be highly suspected when two characteristic phenotype are detected, or a single characteristic lesion is identified in a relative of a known carrier.

Identification of a patient with DICER1 syndrome allows for identification of at-risk family members. However, screening of such individuals screen remains controversial due to the low penetrance. [4,6] Schultz et al propose screening young children known to carry the DICER1 mutation may benefit from a CT chest given that PPB confers the most significant risk of death. [6] Review should be made in conjunction with a medical geneticist.
References


