Cystic nephroma and DICER1 mutations: report of a hitherto unreported mutation

Nefroma quístico e mutações DICER1: relato de uma nova mutação

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ABSTRACT
Paediatric cystic nephroma is a neoplasm of uncertain pathogenesis characterized by a multilocular architecture that develops in children. Some cases may be sporadic, and others may present a familial association, together with other neoplasms, as part of a DICER1 syndrome.
We present a case of a paediatric cystic nephroma with an unreported DICER1 mutation and explore the differential diagnosis mainly with cystic partially differentiated nephroblastoma.

Key words: pathology; mutation; anatomy; histology.

INTRODUCTION
Paediatric cystic nephroma (PCN) is a multilocular neoplasm with fibrous tissue and differentiated tubules that occurs exclusively in children(1).
PCN has an undefined pathogenesis, and it was initially well-thought-out to be a sporadic entity(2). Recent reports describe an association of PCN with pleuropulmonary blastoma in the context of DICER1 mutations(3). Therefore, the identification of these mutations is important in order to provide adequate genetic counselling.

We report the case of a 3-year-old girl with a PCN and an unreported DICER1 mutation.

CASE REPORT
A 3-year-old Caucasian girl was observed by her paediatrician in a routine consultation with a palpable mass in the right upper quadrant. No other symptoms such as abdominal pain, vomiting, diarrhoea, fever, haematuria or other urinary complaints were observed. Blood pressure was normal (< 90th centile for age, gender and height). She was previously healthy and her growth and psychomotor development were normal.

Abdominal ultrasound demonstrated a septated cystic mass with 11 × 10 cm. Thoracoabdominal computed tomography (CT) scan revealed a hypodense and multilocular lesion, which was well-defined, capsulated and expansive in the upper pole of the right kidney with 11 × 10 × 8 cm [length × anteroposterior diameter × width (L × AP × W)], (Figure 1).

FIGURE 1 – CT scan showing a hypodense and multilocular lesion, which is well-defined, capsulated and expansive, located in the upper pole of the right kidney

CT: computed tomography.
The radiology was suggestive of a multicystic renal tumour. Considering the large size of the tumour and the possibility of malignancy, total nephrectomy was performed. There were no complications related to surgery and the patient was discharged home three days later.

Gross examination revealed a right nephrectomy with 450 g and $12 \times 8.5 \times 7$ cm, which on cut section showed a multicystic lesion with $10 \times 8 \times 6.5$ cm, located in the middle and upper portion of the kidney, with smooth inner surface and thin cyst wall (Figure 2). The entire lesion was sectioned and included for microscopic evaluation.

Histological examination was performed on haematoxylin and eosin (HE), stained slides were observed in light microscope – Nikon Eclipse 50i, and images were obtained using a Nikon-Digital Sight DS-Fi1 camera.

Microscopically the cysts were lined by cubic or flat epithelia, sometimes with hobnail cells and prominent nucleoli, but without atypia or mitotic activity (Figure 3A and 3B). The cyst wall was composed of fibrous tissue, with rare, but well-developed renal tubules with mild lymphoplasmacytic inflammation (Figure 3C and 3D). Blastema and muscle/chondroid mesenchymal component were not present. The lesion is well demarcated of non-tumoral renal tissue, without pathological changes.

Final diagnosis of PCN was rendered. This diagnosis, in the setting of a child under 4 years old, may be associated with specific mutations: DICER1 mutations, and consequently clinical implications. Polymerase chain reaction (PCR) was performed on peripheral blood deoxyribonucleic acid (DNA) and a heterozygous mutation was found in the $DICER1$ gene – c.3300dup (p.Ser1101Ilefs*3). This is a pathogenic mutation that forms a premature stop codon that generates a truncated protein\(^{4}\), and has not yet been reported in the literature.

Genetic counselling and testing was offered to the family.

**DISCUSSION**

PCN is an infrequent renal neoplasm, first described by Edmunds in 1892, arising from a group of lesions designated as unilateral multilocular cysts. Only in 1956 the morphological criteria (Boggs and Kimmelstiel) were defined, with posterior modification in 1989 (Joshi and Beckwith)\(^{2,5}\).

It is considered to be related to cystic partially differentiated nephroblastoma and nephroblastoma, despite a characteristic benign nature\(^{20}\).

Although its prevalence is difficult to determine because it is a rare disease, there are two incidence peaks described: one in childhood and the other in adulthood. Most of the cases in childhood occur between ages 3 and 4, with a male predominance\(^{1,2}\). Clinical presentation is normally incidental – palpable mass, perceived by parents or in routine appointments.
by general practitioners or paediatricians; radiological studies show a well-circumscribed, encapsulated and multicystic tumour, however it has no power in the differential diagnosis between PCN and cystic partially differentiated nephroblastoma(2).

Differential diagnosis requires some specific attention to gross examination and extensive sampling, with total inclusion of the lesion. It is mandatory to assess the presence or the absence of blastemal components between the cysts(6, 7).

DICER1 mutation analysis may also reveal a role in differential diagnosis with a sturdier association with PCN, but without association with cystic partially differentiated nephroblastoma. This different association may represent evidence that they are in fact two different diseases and not two spectra of the same(5, 6).

The pathogenesis is uncertain. Germline mutations of DICER1 have been implied in a spectrum of different tumours in children and young adults: pleuropulmonary blastoma, cystic nephroma, cervical rhabdomyosarcoma, multinodular goiter with or without papillary thyroid carcinoma, ovarian steroid cell tumours, among others – condition designed as DICER1 syndrome (1, 5, 8). Genetic counselling is therefore highly recommended in order to identify patients with high risk for active surveillance, which will allow the identification of lesions at low grades/low stages in order to treat them early.

International consensus on surveillance for DICER1 pathogenic variant carriers has not yet been established.

Described recommendations include a chest CT at birth/diagnosis followed by chest radiograph each six months from diagnosis until age 8, and annually from age 8 to age 18; abdominal/pelvic ultrasound from birth/diagnosis each six months until age 40; clinical examination of thyroid annually since age 10 and thyroid ultrasound if justified; among others suggested by clinical assessment(9).

PCN is normally not a life-threatening condition; however these patients can develop aggressive tumours(4) and may benefit from early interventions, namely hysterectomy and thyroidectomy.

CONCLUSION

We present a case of PCN developed in the context of a hitherto unreported DICER1 mutation. Acknowledgement of the association between these mutations and PCN is essential in order to order genetic study and identify at-risk patients for personalised surveillance.

REFERENCES


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