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Nasal chondromesenchymal hamartomas arise secondary to germline and somatic mutations of *DICER1* in the pleuropulmonary blastoma tumor-predisposition disorder

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Abstract

Background—Nasal chondromesenchymal hamartoma (NCMH) is a rare nasal tumor that typically presents in young children. We previously reported on NCMH occurrence in children with pleuropulmonary blastoma (PPB), a rare pulmonary dysembryonic sarcoma that is the hallmark neoplasm in the PPB-associated *DICER1* tumor predisposition disorder.

Methods—Original pathologic materials from individuals with a PPB, PPB-associated tumor and/or a *DICER1* mutation were centrally reviewed by the International PPB Registry. Paraffin-embedded NCMH tumor tissue was available in three cases. Laser-capture microdissection was used to isolate mesenchymal spindle cells and cartilage in one case for Sanger sequencing of *DICER1*.

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WEB RESOURCES

Catalogue of somatic variants in cancer (COSMIC): <http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/>

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Results—Nine patients (5F/4M) had PPB and NCMH. NCMH was diagnosed at a median age of 10 years (range 6-21years). NCMH developed 4.5 - 13 years after PPB. Presenting NCMH symptoms included chronic sinusitis and nasal congestion. Five patients had bilateral tumors. Local NCMH recurrences required several surgical resections in two patients, but all nine patients were alive at 0 – 16 years of follow-up. Pathogenic germline *DICER1* mutations were found in 6/8 NCMH patients tested. In 2 of the patients with germline *DICER1* mutations, somatic *DICER1* missense mutations were also identified in their NCMH (E1813D; n=2). Three additional PPB patients developed other nasal lesions seen in the general population (a Schneiderian papilloma, chronic sinusitis with cysts, and allergic nasal polyps with eosinophils). Two of these patients had germline *DICER1* mutations.

Conclusion—Pathogenic germline and somatic mutations of *DICER1* in NCMH establishes that the genetic etiology of NCMH is similar to PPB, despite the disparate biological potential of these neoplasms.

Keywords

Nasal chondromesenchymal hamartoma; *DICER1*; Pleuropulmonary blastoma

INTRODUCTION

Nasal chondromesenchymal hamartoma (NCMH) was first described in 1998 as a rare nasal tumor that typically presents as a unilateral mass in children (McDermott et al. 1998). A mixed mesenchymal pattern of chondroid and/or osseous islands of tissue with a variably cellular stroma characterized the morphologic features. The lesion may be expansile and locally destructive, with extension into the intracranial space (Kim et al. 2004). In that initial report, there was a child with NCMH and pleuropulmonary blastoma (PPB, “case 7”). The co-existence of these two very rare tumors prompted the authors of that first report to speculate about a possible etiologic association (McDermott et al. 1998). A 15-year-old girl with NCMH and PPB (as well as a “testosterone-secreting left ovarian stromal tumor”) was reported in 2007 (Johnson et al. 2007). The report of four additional children with both NCMH and PPB strengthened this putative association (Priest et al. 2010).

Pleuropulmonary blastoma, a rare pediatric dysembryonic sarcoma of the lung and pleura (Manivel et al. 1988), is the hallmark tumor in the PPB-associated *DICER1* tumor predisposition disorder (OMIM 601200). Approximately 65% of patients with this incompletely penetrant syndrome harbor mutations in *DICER1* (Hill et al. 2009). *DICER1* is an RNase endoribonuclease that catalyzes the cleavage of double-stranded RNA to produce mature microRNAs (miRNAs) and short interfering RNAs (siRNAs) which post-transcriptionally modulate gene expression. Individuals with germline *DICER1* mutations are at increased risk of developing a variety of tumors, including PPB (Hill et al. 2009). Since the initial report of seven cases of NCMH, there are approximately 25 cases reported relative to various aspects of this tumor with its predilection for children 12 months of age or less (Mattos and Early 2011), (Greci et al. 2011), (Yao-Lee et al. 2011), (Uzomefuna et al. 2012), (Cho et al. 2013), (Li et al. 2013a), (Li et al. 2013b). None of these reports made reference to *DICER1* status. Another report described an 11-year-old boy with a history of

PPB at age three years, who presented with nasal obstruction and whose NCMH had a somatic, balanced t(12;17) (q24;q21) translocation (Behery et al. 2012).

In this paper, we report the results of germline and tumor *DICER1* mutation testing in nine patients with NCMH from the International PPB Registry: we include the four previously reported patients (Priest et al. 2010) with NCMH, and describe five new patients with NCMH and PPB. We also describe three PPB patients who developed other nasal lesions, indicating that in PPB patients nasal polyps are not invariably NCMH.

METHODS

The International PPB Registry (IPPBR), founded in 1988, is a collaboration of the Department of Pediatric Hematology and Oncology at Children's Hospitals and Clinics of Minnesota (Minneapolis, MN), the Department of Surgical Pathology at Children's National Medical Center (Washington, DC) and the Department of Pathology and Immunology at Washington University Medical Center (St. Louis, MO). Additional patients were evaluated at the Clinical Center of the National Institutes of Health (Bethesda, MD) through the “*DICER1*-related PPB Cancer Predisposition Syndrome Natural History Study” (National Cancer Institute (NCI) Protocol 11-C-0034; NCT-01247597) at the NCI. The Institutional Review Board at each institution approved this study; all patients (and/or parents) gave written consent to participate.

Individuals referred to the IPPBR and/or NCI study with a PPB, a PPB-associated tumor and/or a *DICER1* mutation are accessioned consecutively. Select patients are evaluated at the NCI and receive a history and physical, imaging, lab work and sub-specialty consultation. Data on clinical presentation, imaging, pathologic materials, family history, treatment and long-term follow-up are collected on IPPBR and NCI enrollees. All pathologic materials submitted to the IPPBR, including the NCMH and non-NCMH nasal lesions in this report, were centrally reviewed by IPPBR pathologists (DAH and LPD).

DNA was extracted from peripheral blood leukocytes for assessment of germline *DICER1* mutations. Formalin-fixed, paraffin-embedded blocks (FFPE) of NCMH were available in three cases. From each of these blocks, four 10-micron scrolls were prepared. Following paraffin removal, DNA was extracted using the Maxwell 16 Formalin-Fixed Paraffin-Embedded Tissue LEV DNA Purification Kit (Promega, Madison, WI) on the Maxwell 16 Instrument (Promega). DNA quality and quantity was assessed using a Nanodrop (ThermoFisher, Wilmington, DE) and Qubit (Qubit 2.0, Life Technologies) respectively. We performed laser-capture microdissection to selectively separate cystic epithelium and underlying mesenchyme and cartilage on one of the NCMH tumors (Table 1, case 6), (mmiCellCut Plus, Molecular Machines and Industries, Inc., Haslett, MI). A minimum of 100 cells was captured from epithelium and mesenchyme/cartilage respectively. DNA extractions were performed using QIamp DNA FFPE kit (Qiagen, Valencia, CA).

For germline *DICER1* sequencing, the coding region of *DICER1* was sequenced and analyzed for variants as described previously (Hill et al. 2009). For tumors, DNA was sequenced using primer pairs for small amplicons containing the codons for amino acids

1705, 1709, and 1809, 1810, 1813, and 1814, each covering a somatic missense hotspot seen in PPB (Pugh et al. 2014): Primer pair 1: Forward: 5'-tgggatcagttgctatgtg-3' and Reverse: 5'-CGGGTCTTCATAAAGGTGCT-3'; Primer pair 2: Forward: 5'-tggactgcctgtaaaagtg-3' and Reverse: 5'-ATGTAAATGGCACCAGCAAG-3'. The sequence traces were assembled and the chromatograms were scanned for variants using Sequencher version 5.1.

RESULTS

Nine patients (five females and four males) with PPB were diagnosed with NCMH at a median age of 10 years (range 6-21 years). Presenting NCMH symptoms included chronic sinusitis and nasal congestion; five patients had bilateral tumors (Table 1). Three patients had cystic PPB (Type I and a lung cyst that was not examined microscopically); six patients had solid PPB (Type II, II/III and III). NCMH developed 4.5 - 13 years after PPB diagnosis. Two patients (#1 and #9) had local NCMH recurrence (4 and 1 recurrences) requiring additional surgical resections. All nine NCMH patients were alive at 0 – 16 years of follow-up. Seven patients with PPB Types I, II or III received chemotherapy before developing NCMH. One patient with Type I PPB and the patient with the lung cyst received no chemotherapy. Patient #7 received radiation therapy to the chest.

The pathological features of NCMH cases in this report were similar. Each showed a polypoid mass or masses containing variably-sized cysts lined by respiratory epithelium. Nodules of immature or mature cartilage were surrounded by spindle cell mesenchyme. The polyp matrix contains a loose myxoid ground substance containing inflammatory cells, small vessels and variable amounts of fibrosis. Interestingly the NCMH from patient #9 in this report lacked cartilage nodules (Figure 1).

Patients #10, #11 and #12 had other nasal pathology including, respectively, a Schneiderian papilloma, chronic sinusitis with cysts, and allergic nasal polyps with eosinophils (Table 1 and Table 2). Tissue from the Schneiderian papilloma was available for *DICER1* sequencing; no somatic mutations were found. Tissue from the other two cases was not available for *DICER1* sequencing. All three had a history of Type I PPB (Hill et al. 2008). None were treated with chemotherapy or radiation.

Germline mutations in *DICER1* were observed in 6/8 (75%) NCMH patients tested and in 2/3 of the patients with other nasal lesions (Table 2).

DICER1 somatic mutations were seen in all 3 NCMH tissues tested (Table 2); adequate materials for somatic *DICER1* sequencing were not available from the non-tested NCMH. The *DICER1* somatic mutation NM_177438.2:c.5439G>T, p.Glu1813Asp (E1813D) was identified in laser-dissected mesenchymal spindle cells and cartilage but not epithelium from patient #6, indicating that there is a clonal population of tumor cells in mesenchyme, similar to the early pathogenesis of PPB. The same exact base substitution was seen in the NCMH from patient #9 and the same amino acid was affected in patient #2, c.5437G>A; p.Glu1813Lys (E1813K). Patient-specific germline *DICER1* mutations were detected in tumor tissue in patients #6 and #9.

DISCUSSION

In this paper, we expand on our prior report of four PPB patients to nine who have developed NCMH and provide evidence that the genetic pathogenesis of this benign tumor mirrors that of PPB (Priest et al. 2010). Out of 405 central pathology-confirmed PPB registered by the IPPBR we are aware of eight (2%) who developed NCMH. Since NCMH appears to occur at a later age than PPB, the prevalence of NCMH in patients with PPB enrolled in the IPPBR may be underestimated; long term follow-up is required to permit for accurate estimation of this parameter. At this time, there are no formal screening recommendations for NCMH in *DICER1* carriers. In patients of all ages with a *DICER1* mutation (or with a *DICER1*-associated tumor), a review of systems pertaining to nasal masses is appropriate: are there respiratory or feeding difficulties, rhinorrhea, epistaxis, nasal obstruction, snoring, mouth breathing, hyponasal speech, visual disturbances, headache or otitis media? On exam, evidence of orbital involvement of the tumor (*e.g.*, ptosis, hypotropia, ophthalmoplegia) should be noted. In our experience, nasal endoscopy in the clinic (with topical anesthesia) and/or maxillofacial computed tomography (CT) are both effective means of NCMH detection. All of the NCMH cases seen to date in the PPB syndrome have followed a benign course. Surgical removal is curative, although local recurrences can be seen as was the case in two of nine patients discussed here. This appears to be similar to the historical experience with *DICER1*-associated cystic nephroma (CN) and in contrast to the natural history of lung cysts where there is a known risk for progression to high grade sarcoma (Priest et al. 1997; Priest et al. 2006). As a potential note of caution, sarcomatous transformation in CN has been recently described in *DICER1* mutation carriers (Doros et al. 2014) and a recent report documents one adult patient with malignant transformation in an NCMH (Li et al. 2013b).

Not all nasal lesions in children with PPB and/or *DICER1* mutations are NCMH. Patient 10 in our cohort was diagnosed with a ~2 cm Schneiderian papilloma, inverted type, with its origin from the lateral nasal wall. These lesions are benign epithelial neoplasms arising from the Schneiderian mucosa (an ectodermally derived respiratory mucosa) of the sinonasal tract. Chronic sinusitis appears to be a risk factor for Schneiderian papilloma. Tumor tissue for *DICER1* sequencing for this case was not available. We are not aware of any other published associations between Schneiderian papillomas and PPB or *DICER1* mutations. Patient 10 had a long history of allergic sinusitis prior to the diagnosis of the Schneiderian papilloma. The other two patients with PPB and non-NCMH nasal masses had chronic sinusitis with polyps, one of which had cysts. The pathologic differentiation of NCMH from inflammatory polyps may be difficult since fewer than 20 cases have been reported in the literature and the full spectrum of morphologic change in NCMH may be unknown. This is demonstrated by one case which was previously diagnosed as “respiratory epithelial adenomatoid polyp” only later to be confirmed as NCMH that lacked cartilage. Schneiderian papillomas, allergic sinusitis and chronic sinusitis with polyps occur in the general population; our data are insufficient to suggest that patients with a *DICER1* mutation have a higher incidence of non-NCMH pathology.

PPB has a purely cystic form: Type I, and Type I regressed (Ir) PPB (Hill et al. 2008); a solid/cystic form (Type II), and a completely solid form (Type III). The outcome of cystic

form Type I or Ir is better than the outcome for Types II and III (Messinger et al. 2012; Williams et al. 2012). The list of other *DICER1*-associated tumors continues to grow and includes CN (Bahubeshi et al. 2010), familial multinodular goiter with and without Sertoli-Leydig cell tumors (SLCT) (Rio Frio et al. 2011), Wilms tumor (Foulkes et al. 2011), ciliary body medulloepithelioma (Slade et al. 2011), botryoid-type embryonal rhabdomyosarcoma (ERMS) of the uterine cervix (Doros et al. 2012), and pineoblastoma (Sabbaghian et al. 2012). However, phased (determination of *cis* or *trans*) biallelic *DICER1* mutations or loss of heterozygosity of *DICER1* has been established only in Wilms tumor (Wu et al. 2013), pineoblastoma (Sabbaghian et al. 2012), SLCT (Heravi-Moussavi et al. 2012), primitive germ-cell tumor of the yolk-sac type (Heravi-Moussavi et al. 2012) and PPB (Pugh et al. 2014). Somatic missense mutations of certain “hotspot” residues (E1705, D1709, G1809, D1810 and E1813) have been detected in CN (Doros et al. 2014), SLCT, nonseminomatous testicular germ-cell tumors, ERMS and rare epithelial ovarian and endometrial carcinomas (Heravi-Moussavi et al. 2012) and PPB (de Kock et al. 2013; Pugh et al. 2014). The hotspot mutations affect amino acids in the *DICER1* RNase IIIb domain, the protein site that is critical for miRNA interaction and cleavage of mature miRNA from the 5' arm of the precursor miRNA hairpin.

Germline mutations in *DICER1* were identified in 6/8 (75%) NCMH patients evaluated. Somatic mutations involving glutamine at hotspot position 1813 in the RNase IIIb domain of *DICER1* were detected in all three NCMH tumors tested. We did not specifically test if the position E1813 mutations are on the wild-type chromosome in NCMH (in *trans*) with the known germline *DICER1* mutation in the patients. However, other hotspot residues have been shown to be in *trans* with a germline *DICER1* mutation; in SLCT and primitive germ-cell tumor of the yolk-sac type (Heravi-Moussavi et al. 2012) and PPB (Pugh et al. 2014), phased biallelic mutations in *DICER1* have been found. In these tumor types, the investigators established that the hotspot residue D1709 was somatically mutated.

Somatic mutations of *DICER1* E1813 have been described previously in *DICER1*-familial PPB tumor predisposition syndrome tumors. The E1813 amino acid residue is invariably conserved, including in *S. pombe*, *G. intestinalis*, *T. maritime* and *E. coli* (Takeshita et al. 2007). Three SLCT with somatic mutations (only) affecting *DICER1* residue E1813 (E1813Q, E1813G, E1813K) and one SLCT with a germline *DICER1* mutation and a somatic *DICER1* E1813K mutation have been reported (Heravi-Moussavi et al. 2012). In a 3-year-old child with a Type II PPB, a pathogenic *DICER1* germline mutation and a somatic *DICER1* E1813G mutation were found, although phase was not determined (de Kock et al. 2013). Tumor sequencing in 51 PPBs found two somatic *DICER1* E1813D, E1813G, E1813K, and E1813Q in 4%, 10%, 2% and 2% of PPBs respectively (Pugh et al. 2014). Sanger sequencing of the RNase IIIa and IIIb domains in *DICER1* in a collection of 154 gonadal tumors uncovered somatic E1813K, E1813Q and E1813D mutations in three different SLCT (Witkowski et al. 2013). In the online Catalogue of Somatic Mutations in Cancer (COSMIC, accessed 10/10/13), there were two E1813Q variants in a colorectal carcinoma, one E1813G variant in an endometrial carcinoma and one E1813A variant in an endometrial carcinoma.

RNase III enzymes like DICER1 cut miRNAs and require divalent metal ions, with Mg²⁺ as the preferred species; in the RNase IIIb domain, amino acid residue E1813 serves as a magnesium-binding site and is invariably conserved (Takeshita et al. 2007). In PPB, the pathogenic mutations in *DICER1* hot-spot residues E1705, D1709, G1809, D1810 and E1813 have been shown to disrupt the cleavage of the 5p miRNA from the precursor miRNA hairpin (Pugh et al. 2014). The miRNA sequence shows normal mature 3p miRNA but the 5p miRNA retains the hairpin sequence (Pugh et al. 2014). Presumably these 5p miRNAs with retained hairpin sequence are non-functional. Coupled with a loss-of-function mutation on the other *DICER1* allele (germline mutation in many cases), these specific somatic mutations contribute to defective repression of genes regulated by 5p miRNAs.

In summary, we found germline *DICER1* mutations in 6/8 evaluated patients with NCMH. In the NCMH of two of the six patients with *DICER1* germline mutations, we found somatic *DICER1* E1813D mutations, a known pathogenic missense variant. Another known somatic *DICER1* missense variant, E1813K, was also detected in the NCMH of a third patient without a known germline *DICER1* mutation. Detecting pathogenic somatic and germline mutations in *DICER1* establishes genetic proof of a tumor association with the gene. NCMH should be considered as part of the *DICER1* tumor spectrum.

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Figure 1.

Nasal chondromesenchymal hamartoma from Patient #9. This patient had multiple sinonasal polyps featuring cysts lined by respiratory epithelium in an inflamed fibrous stroma. This case was unusual in that it lacked cartilaginous nodules. H&E; Original magnification 20x.

Table 1

Nasal chondromesenchymal hamartoma (NCMH) and other nasal pathologies in patients with a *DICER1* mutation or history of PPB.

Patient Number/Gender	Age at NCMH/Nasal Tumor Diagnosis (years)	Symptoms	Pathology	Laterality	Recurrence	Follow-up from NCMH/Nasal Tumor Diagnosis (months)	Initial PPB Type	Age of Diagnosis of PPB (months)	Time from PPB to NCMH (months)
1 * /Male	7	Nasal congestion; mother noted nasal mass	NCMH	Initially unilateral; bilateral at recurrence	Multiple	190	II-III NOS	33	54
2 * /Female	15	Chronic sinusitis, facial pain and nasal congestion	NCMH	Bilateral	None	88	II	22	156
3 * /Female	10	Nasal congestion	NCMH	Bilateral	None	41	III	40	81
4 * /Male	11	Nasal congestion	NCMH	Right	None	32	III	54	83
5 /Male	8 (105 mo)	ND	NCMH	ND	None	17	I	0	105
6 /Female	13 (157 mo)	ND	NCMH	Bilateral	None	10	II	70	87
7 /Male	8 (101 mo)	Chronic sinusitis	NCMH	Bilateral	None	28	II	40	61
8 /Female	6 (82 mo)	ND	NCMH	ND	None	1	I	0	82
9 /Female	21 and 25	At 21 yrs: nasal congestion and septal deviation. Recurrent lesion: nasal obstruction	NCMH	Right	Yes	18 mo (since surgery at age 25 yrs)	Lung cyst	324 (27 yrs)	NA
10 /Male	23 (277 mo)	Worsening congestive and obstructive symptoms; evaluation by endoscopy revealed a mass in left nostril	Schneiderian papilloma, inverted type	Unilateral	None	3	Ir	204	73
11 /Female	17 (206 mo)	ND	Chronic sinusitis, with cysts	Bilateral	NA	0	Ir	30	176
12 /Female	27	Chronic sinusitis unresponsive to multiple courses of antibiotics. Mass in right ethmoid sinus detected on screening nasal endoscopy.	Allergic nasal polyp with eosinophils	Right	None	6	Ir	324 (27 yrs)	NA

NA: not applicable; ND : no data

* Patients 1–4 previously reported by us (Priest et al. 2010) (case numbering retained). Patients 10–12 were suspected of having an NCMH but were determined to have other nasal pathology.

Table 2

Germline and somatic *DICER1* status in NCMH and nasal tumor cohort.

Patient Number/Gender	<i>DICER1</i> Mutation (Germline)	<i>DICER1</i> Status (Somatic)	Associated Findings (in addition to PPB and NCMH)
NCMH Patients			
1/Male	c.2863delA; p.T955fs	ND	Lung cysts contralateral to PPB
2/Female	ND	c.5437G>A; p.Glu1813Lys	Sertoli-Leydig cell ovarian tumor
3/Female	c.2040+1G>T; splice	ND	None
4/Male	c.4407_4410delTTCT; p.L1469fs	ND	None
5/Male	Negative	ND	Bilateral pulmonary cysts in utero; jejunal polyps
6/Female	c.1376+1G>T	LMD c.5439G>T; p.Glu1813Asp (mesenchyme and cartilage only)	Thyroid papillary carcinoma; Sertoli-Leydig tumor
7/Male	c.5394delA	ND	
8/Female	Negative	ND	Left cystic nephroma; small bowel polyp
9/Female	c.3726C>A; p.Y1242X	c.5439G>T; p.Glu1813Asp	Sertoli-Leydig cell tumor at age 13 years; multi-nodular goiter
Other Nasal Lesions			
10/Male	p.Y749X	No <i>DICER1</i> mutation detected; (Schneiderian papilloma, inverted type)	Unilateral/multifocal lung cysts; thyroid nodules
11/Female	Negative	ND; (Chronic sinusitis, with cysts)	Cystic nephroma; detached retina; pineoblastoma; papillary carcinoma; Sertoli-Leydig cell tumor; CBME
12/Female	c.3019C>T; p.Q1007X	ND; (Allergic nasal polyp with eosinophils)	Multi-nodular goiter status-post total thyroidectomy at 21 y/o; recurrent pansinusitis

LMD = laser-capture microdissection; ND = no data; CBME = ciliary body medulloepithelioma