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SINE QUA NON RADIOLOGY-PATHOLOGY

Nasal Chondromesenchymal Hamartoma

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Abstract
Nasal chondromesenchymal hamartoma (NCMH) is a rare, benign lesion of the sinonasal tract. It usually presents as a polypoid mass in infants and older children. Imaging studies and endoscopy are required to delineate the extent of the lesion and aid in its excision. This unusual lesion is composed of proliferating mesenchymal and cartilaginous elements. Recently, a genetic association between NCMH and *DICER1* mutation has been established. It is important for pathologists to be familiar with this entity to avoid misdiagnosis since the lesion is benign and surgical excision is curative.

Keywords Nasal polyps · Hamartoma · DICER1 protein

Case Presentation

A three-month-old male child presented with difficulties breathing, especially when feeding, since birth. The child was born by caesarean section because of failed induction. At birth, the baby had transient hypoxia which was relieved after oxygen therapy.

Radiology

In light of progressive respiratory distress, computed tomography (CT) scan was performed. It showed a homogeneously enhancing, lobulated mass lesion filling the left nasal cavity that measured approximately 3.0 × 2.5 cm (Fig. 1a). No calcifications or necrosis was seen within the lesion. The mass caused significant deviation of the nasal septum to the right, lateral bowing of the medial wall of the left orbit, and inferior bowing of the left palate (Fig. 1b). Superiorly, the lesion extended to the floor of the posterior ethmoid sinuses. No intracranial or intraorbital extension was observed. Posteriorly, the lesion reached the choana, and, anteriorly, the left nasal bone which showing mild anterior bowing. Bony erosion was not seen in any of the visualized facial bones. On magnetic resonance imaging (MRI), the lesion was hyperintense in the T2-weighted-Fluid-Attenuated Inversion Recovery (FLAIR) images (Fig. 1c, d). The visualized brain sections were unremarkable.

Diagnosis and Treatment

The child was then assessed by endoscopy which reveal a polypoid mass arising from the skull base, lateral to the middle turbinate, that completely occupied the left nasal cavity. It had a bluish hue and prominent vessels. The mass was pushing the nasal septum to the right side. The polyp was completely excised by a transnasal approach and sent for histopathologic examination.

Grossly, the excised lesion was polypoid and firm with a shiny outer surface containing congested vessels. The cut surface was brown in color. Histologic examination showed respiratory epithelium surfacing a polypoid proliferation of sheets and whorls of oval to plump stromal cells in a haphazard arrangement. Collagen bundles and hyalinised stroma were admixed with the stromal cells (Fig. 2). These cells had dispersed nuclear chromatin with inconspicuous nucleoli and scant cytoplasm. Multiple islands of mature cartilage containing benign chondrocytes were

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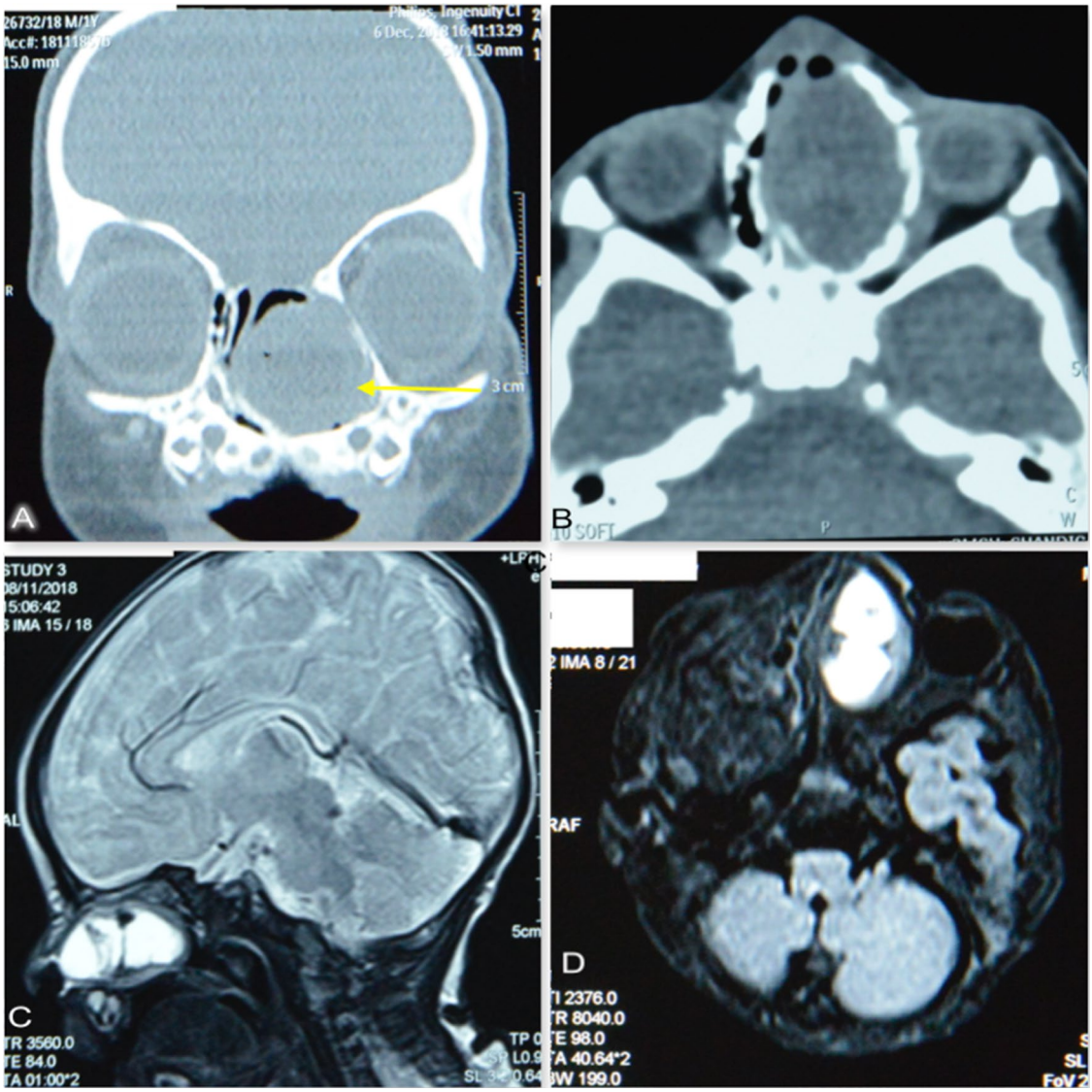

Fig. 1 Imaging findings of NCMH. **a** CT scan shows a lobulated mass in the left nasal cavity (arrow pointed) with near complete occlusion of the lumen. **b** Axial sections shows deviation of the nasal septum to the right side and lateral bowing of the medial wall of the left orbit. **c**, **d** MRI T2/FLAIR images show hyperintensity of the lesion to the normal brain parenchyma

present with focal osteoid formation (Fig. 3a, b). There was no cellular atypia, mitotic activity, or necrosis. No epithelial component, meningothelial cells, neural tissue, or any other mesenchymal element was identified.

The stromal cells were diffusely positive for vimentin (cytoplasmic) (Fig. 3c) and S-100 (nuclear and cytoplasmic). The S100 stain also highlighted chondrocytes (Fig. 3d). Immunohistochemical stains for epithelial membrane antigen (EMA), glial fibrillary acidic protein (GFAP), INI-1, desmin, myogenin, MyoD1, smooth muscle actin, CD34, brachyury, cytokeratin, STAT6, and SATB2 were negative. A MIB-1 labeling index was less than 1%. The final diagnosis was nasal chondromesenchymal hamartoma.

Discussion

The differential diagnosis of a polypoid nasal mass includes sinonasal inflammatory polyp, meningocoele, encephalocoele, nasal glial heterotopia, teratoma, nasal dermoid cyst, nasopharyngeal angiofibroma, inverted sinonasal papilloma, chordoma, olfactory neuroblastoma, and, rarely, embryonal rhabdomyosarcoma [1].

Histologically, an inflammatory polyp was excluded due to the lack of mixed inflammatory cell infiltrate, edematous stroma, and thickened basement membrane. No meningothelial cell proliferation or glial background was present, as demonstrated by negative EMA and GFAP

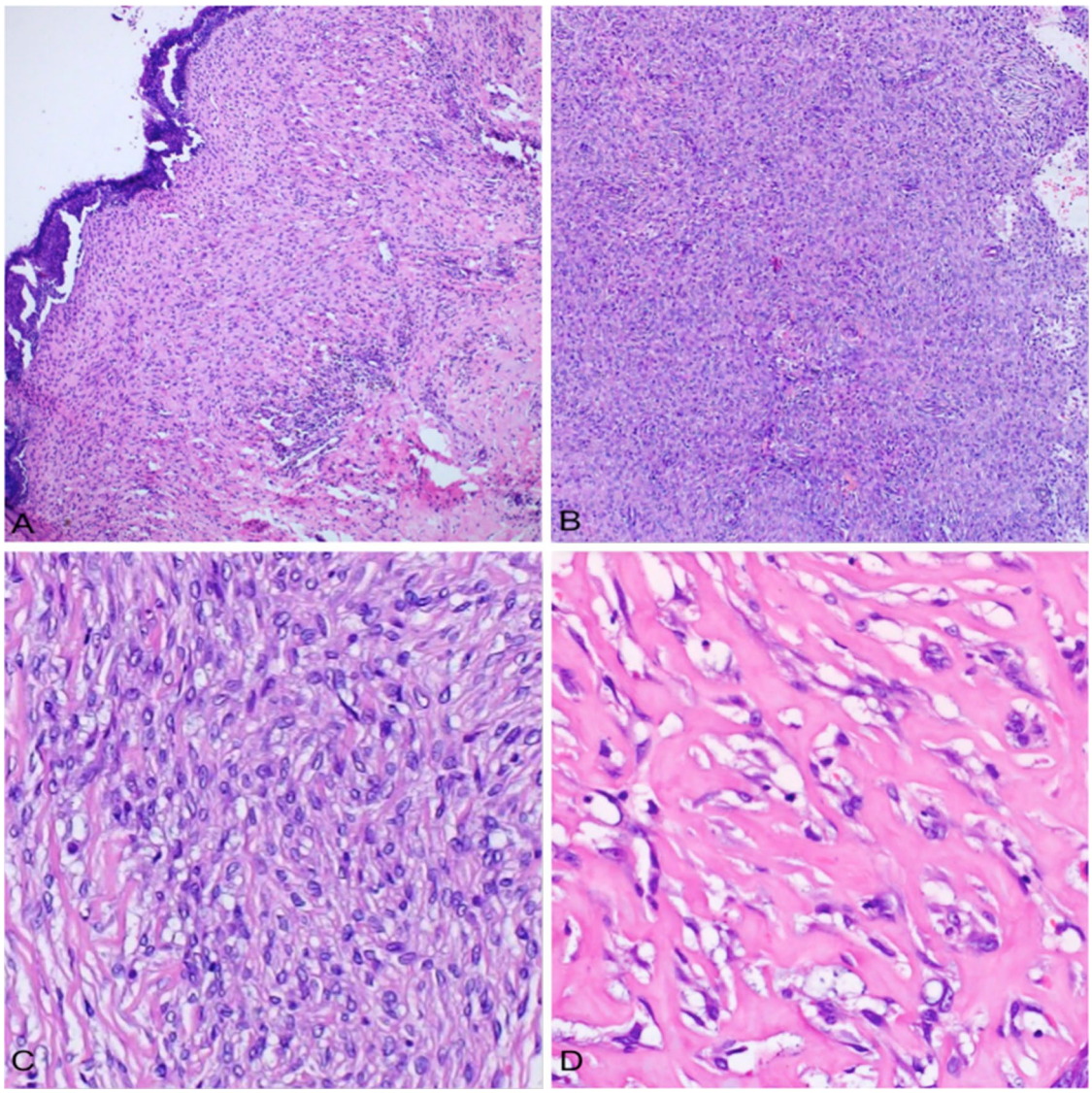

Fig. 2 Histopathologic findings. **a** A polypoid mass surfaced by respiratory epithelium (×10 magnification). **b** Subepithelium with sheets and whorls of oval to spindle cells (×20 magnification). **c** The cells have round to oval nuclei with fine, dispersed chromatin (×20). **d** Few areas showed dense collagenous stroma admixed with stromal cells (×40)

immunostains, ruling out meningocoele and nasal glial heterotopia, respectively.

The mesenchymal cells were histologically bland and did not show features of malignancy such as hyperchromasia, atypia, mitotic activity, or necrosis. Additionally, desmin, myogenin, and MyoD1 immunostains were negative to exclude rhabdomyosarcoma. No embryonal cells, rosettes, or neuropil material were present to suggest an olfactory neuroblastoma. Neuron specific enolase (NSE) was also negative, ruling out this entity.

INI-1 deficient intracranial sarcoma is a recently reported tumor in young adults. The cells have a spindled to rhabdoid morphology with loss of INI-1 expression. Though the profile did not fit with our presentation, INI-1 immunostain was performed and its expression was retained, excluding this diagnosis.

After excluding common entities, the presence of disorganized cartilaginous islands and osteoid brought us close to the diagnosis of NCMH. Histologically, only a few lesions show bland oval to spindled cells with cartilage and bony trabeculae formation. These include nodular fasciitis and fibro-osseous dysplasia which are site specific and have characteristic histologic features that were lacking in this case [2]. Chordoma can also show chondroid stroma and rarely presents as a nasal polyp; however, owing to lack of classical morphology, physaliferous cells, and brachyury reactivity, this diagnosis was also ruled out.

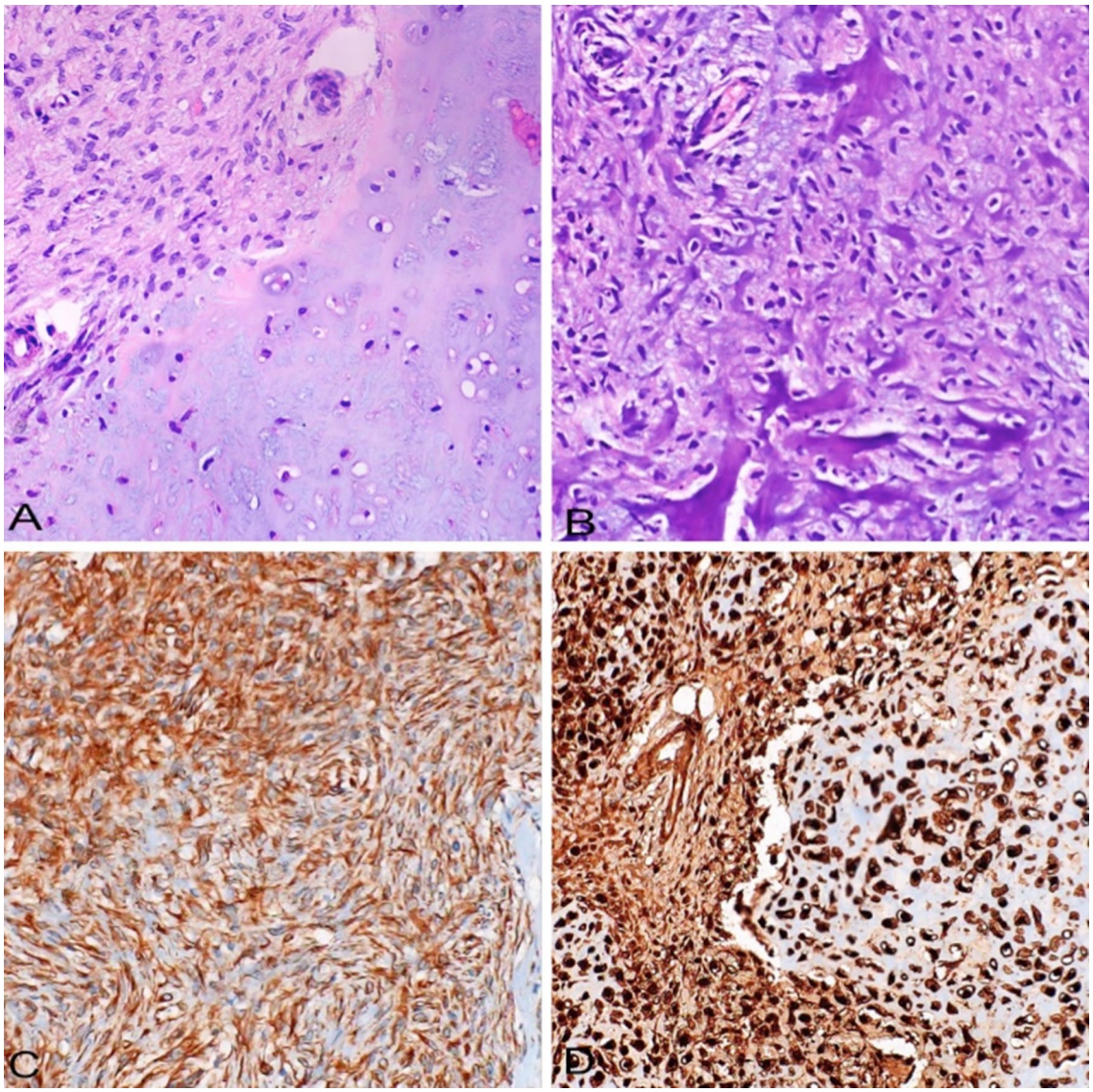

Fig. 3 Histopathologic findings. **a** Interface of mature cartilage and the stromal cells (×20 magnification). **b** Osteoid formation within the lesion (×20 magnification). **c** Vimentin immunostain shows diffuse positivity in the oval and spindle cells (×20). **d** S-100 stain shows diffuse positivity (nuclear and cytoplasmic) in the stromal cells and cartilage (×20)

NCMH was first reported in 1998 by McDermott et al. who described it as a "hamartoma analogous to a chest wall mesenchymal hamartoma". It is extremely rare and approximately 50 cases are reported in the literature [3]. The exact origin of this tumor is unknown, but it is hypothesized to derive from embryologic rests. Although NCMH usually presents in infants, a few cases have been reported in adults. The mean age of presentation is 9.6 years with a range from birth to 69 years. There is a male predilection with a male to female ratio of 2.2:1 [4]. In light of a history of neonatal asphyxia and progressive respiratory distress, this case may be considered a congenital NCMH.

NCMH typically arises from the nasal septum or vestibule. Other affected sites include the maxillary and ethmoid sinuses, orbit, nasopharynx, and oropharynx. The clinical presentation may vary from asymptomatic to nasal obstruction with mass effect. Rarely, ocular symptoms may develop with large lesions [4]. While NCMH is benign, a locally destructive lesion may cause concern for malignancy. An encephalocoele may be a diagnostic consideration in cases with intracranial extension [2, 5]. In our case, however, the mass was well circumscribed without intracranial extension.

Histologically, this case exemplified the features most characteristic of NCMH. There were prominent islands of hyaline cartilage, spindle to oval mesenchymal cells in a myxoid background, and focal osteoid formation. In addition to these classic findings, diverse histologic features such

as osteoclastic giant cells, aneurysmal bone cyst-like areas, adipose tissue, and fascicles of fibrous tissue are reported.

The classification of mesenchymal hamartomatous lesions of the nasal cavity is unclear due to a lack of universally accepted nomenclature and incomplete understanding of the pathogenesis. NCMH has been previously described in the literature as chondroid hamartoma, nasal hamartoma, and mesenchymal hamartoma [6].

The presence of a *DICER1* germline mutation in some NCMHs raises an association with a family of tumors harboring mutations in this gene. The hallmark tumor in *DICER1* tumor predisposition disorder is pleuropulmonary blastoma (PPB), a rare pediatric dysembryonic sarcoma of the lung and pleura. Approximately 70% of patients with PPB harbor mutations in the *DICER1* gene [7]. *DICER1*, located on chromosome 14q32.13, is involved in the regulation of miRNA production. Mutations are seen in several tumor types including pituitary blastoma, pineoblastoma, ciliary body medulloepithelioma, embryonal tumor with multilayered rosettes-like infantile cerebellar tumor, primary *DICER1*-associated CNS sarcoma, pleuropulmonary blastoma, cystic nephroma, ovarian sertoli-leydig cell tumor, multinodular goiter/differentiated thyroid cancer, embryonal rhabdomyosarcoma of the uterine cervix, and *DICER1*-associated anaplastic sarcoma of the kidney [8, 9]. The co-existence of PPB and NCMH led McDermott et al. to investigate the association. Later, Priest et al. showed co-existence of the two diseases in four children [3, 10]. In this series, all four patients developed NCMH following the diagnosis of PPB (mean gap 4 to 12 years), and both tumors showed a germline *DICER1* mutation. The authors concluded this finding could indicate clonality of NCMH. In another series of eight NCMH cases, a germline *DICER1* mutation was found in six (75%) [11].

Pediatric oncologists and otorhinolaryngologists should be aware of the possibility of NCMH and PPB association, especially with symptoms of persistent nasal congestion or sinusitis in a treated case of PPB [10]. Patients initially diagnosed with NCMH should also be kept on close follow up as there may be a risk of developing other *DICER1* mutated tumors. This child has no family history of similar lesions or tumors associated with *DICER1* mutations and is on regular follow up. Parameters like cytological atypia, nuclear hyperchromasia, mitotic figures, and increased MIB-1 labeling index should also be assessed as one case report demonstrated malignant transformation [12]. The child in our case is doing well at 9 months follow up, without evidence of recurrence.

This report highlights the radiologic and histopathologic presentation of a classic case of NCMH, a benign hamartomatous lesion cured by surgical excision. Recently, an association has been established between NCMH and *DICER1* mutation. Recognizing this entity is important as the presence of a germline *DICER1* mutation may be associated the development of other tumors.

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Compliance with Ethical Standards

Conflict of interest: No conflict of interest to disclose.

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