

# Malignant transformation of nasal chondromesenchymal hamartoma in adult: a case report and review of the literature

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**Summary.** Nasal chondromesenchymal hamartoma (NCMH) is an extremely rare benign tumor arising in the sinonasal tract, predominantly involving infants and children. To date, only 27 cases are reported in the international literature and there have been no reported cases of malignant transformation. We present a 40-year-old female patient with nasal obstruction and bloody rhinorrhea. Computed tomography (CT) of the nose and paranasal sinuses confirmed a heterogeneous polypoid soft-tissue mass filling the nasal cavity and extending into the maxillary and ethmoid sinus. The patient underwent a complete radical resection. Histological and immunohistochemical analyses showed a portion of the mass was consistent with typical NCMH. However, some areas of mass exhibited cytological atypia, marked mitotic activity and foci of necrosis. The atypical mesenchymal spindle cells were immunoreactive for vimentin, CD99 and smooth muscle actin (SMA) diffusely. The cartilaginous cells were immuno-positive for S-100 protein. Ki-67 index was high in atypical areas, accounting for 50%. A rapid mass recurrence was observed at the original site only 3 months after surgery. The final diagnosis of NCMH with malignant transformation was made. To our knowledge, this is the first report of malignant transformation occurring in an adult with NCMH. Although NCMH commonly develops in the neonate or young infants and exhibits benign histological appearance and favorable prognosis, there is a possibility of malignant transformation in adult patients. Thoroughly histological inspections are suggested to be necessary to accurately diagnose this tumor when it is encountered in adults.

**Key words:** Chondromesenchymal hamartoma, Malignant transformation, Nasal cavity, Adults, Differential diagnosis

## Introduction

Nasal chondromesenchymal hamartoma (NCMH) is an extremely rare benign tumor arising in the sinonasal tract of infants and children. Histologically, NCMH is characterized by a mixture of various mesenchymal elements with bland appearance, including spindle cells, collagen fibers and irregular islands of osseous and chondroid tissue, whose morphological features are similar to the chest wall hamartoma (Jundt et al, 2005). To our knowledge, Twenty-seven NCMH cases have previously been reported in the English literature, and predominantly occur in infants with favorable prognosis (McDermott et al., 1998; Kato et al., 1999; Hsueh et al., 2001; Alrawi et al., 2003; Kim et al., 2004; Norman et al., 2004; Shet et al., 2004; Ozolek et al., 2005; Low et al., 2006; Johnson et al., 2007; Silkiss et al., 2007; Finitis et al., 2009; Kim et al., 2009; Priest et al., 2010; Sarin et al., 2010; Yao-Lee et al., 2011). Herein, we report a case of this clinical entity in a middle-aged female patient. In contrast to previous cases, however, our case presents prominent malignant morphological features and aggressive biological behavior. This is the first presentation of malignant histopathological findings of a NCMH in adult. The literature on this rare tumor is reviewed and differential diagnosis is discussed.

## Materials and methods

### *Clinical history*

A 40-year-old female patient presented with

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complaints of mild headache and left nasal obstruction for 9 months. During this period, she developed fatigue and had gradually weakened smell acuity. A week before admission to our hospital, she was suffering from bloody rhinorrhea and severe headache. As a result, the patient was referred to our hospital for examination and treatment. Physical examination showed that the left nasal cavity was obstructed by a large polypoid mass. The mass filled the left nasal cavity and displaced the nasal septum, and extended into the maxillary and ethmoid sinus. There was no defect in visual field test and vision acuity on her eyes. The laboratory results, including blood count, differential, liver and renal function, were within the normal range. Computerized tomographic (CT) scans revealed a irregular, heterogeneous mass in the left nasal cavity measuring 6.0x4.2 cm. The mass filled the left nasal cavity, displaced the nasal septum, and extended into the bilateral postnasal, left maxillary and ethmoid sinus. The infiltration and destruction of adjacent bony structures and medial wall of left orbit were observed, but there was no intracranial involvement (Fig. 1).

A left lateral rhinotomy with total tumor resection was performed. On surgical excision, the tumor was a noncapsulated, poorly defined mass. The adjacent structures and the medial wall of the left orbit were involved, but no intracranial invasion was observed. Post-operative recovery was uneventful without surgical complications. After diagnosis, the patient refused the radiotherapy/chemotherapy and was only on regular follow-up. A follow-up endoscopic examination at 3 months showed that a mass re-grew at the site of original tumor location. The biopsy revealed the tumor had recurred. Since there was a possibility of distant metastasis to another anatomical location, the patient was referred to a whole body positron emission tomography/computed tomography (PET/CT) study to search for a potential secondary tumor, but no abnormality was found. The patient decided to receive the radiotherapy and chemotherapy. Regretfully, the patient was lost to contact when she was transferred to other hospital.

#### *Procedures*

The surgical specimens and the biopsy from recurred mass were routinely fixed in 10% neutral buffered formalin after tumor resection. The tissues were embedded in paraffin. Four micrometer-thick sections were stained with H&E. Immunohistochemical analyses were performed using the ChemMate Envision/HRP Kit (Dako, Glostrup, Denmark). The antibodies used in this study were cytokeratin (AE1/AE3), vimentin, EMA, S-100 protein, CD99, CD34, CD56, neuron-specific enolase (NSE), synaptophysin (Syn), Bcl-2, smooth muscle actin (SMA), Calponin, desmin, Myo D1, myogenin and Ki-67. The antibodies were obtained from Dako Cytomation (Carpinteria, CA, USA) and Santa Cruz Biotechnology (Santa Cruz, CA, USA).

Slides were dewaxed and rehydrated routinely and then were treated with 10 mmol citrate buffer (pH 6.0) in a microwave for antigen retrieval. After incubation with diluted primary antibodies, slides were treated with the ChemMate Envision/HRP Kit for 30 min at room temperature followed by development with diaminobenzidine (DAB) for visualization. In order to distinguish from synovial sarcoma with bone and cartilage metaplasia, fluorescence in situ hybridization (FISH) assay was performed on paraffin-embedded sections using SYT Dual Color Break-Apart Rearrangement Probe (Vysis, Abbott Laboratories Inc., Maidenhead, Berkshire, UK). Fifty non-overlapping nuclei, which were clearly identified and contained unequivocal signals, were counted for section. A probe was considered to be split when the red and green signals were separated by a distance greater than the size of one fusion yellow signal. A positive result was identified when 20% or more single nuclei were found to harbor both a fusion and split (break-apart) signals.

#### **Results**

##### *Microscopic findings*

Under microscopic examination, small areas showing the typical morphology of NCMH were recognized in mass. In these areas, islands of benign hyaline cartilage along with spindle cells and dense collagen were noted. The bland cartilage and spindle cells were mildly hypercellular without appreciable cytological atypia or pleomorphism. Mitotic figures were not present in these areas (Fig. 2A). However, most areas of the mass were composed of hypercellular plump spindle tumor cells with conspicuous nucleoli and indistinct boundaries. Many mitotic figures (more than 20 mitotic figures per 10 high power fields), including pathological mitotic forms, were evaluated among the spindle tumor cells (Fig. 2B). Histological progression from bland areas to atypical areas could be observed in the tumor. The irregular islands of cartilage contained large, occasional binucleate chondrocytes with conspicuous nucleoli. Mitotic figures were also observed in cartilage (Fig. 2C). Moreover, foci of necrosis were identified in the tumor (Fig. 2D).

##### *Immunohistochemical and FISH findings*

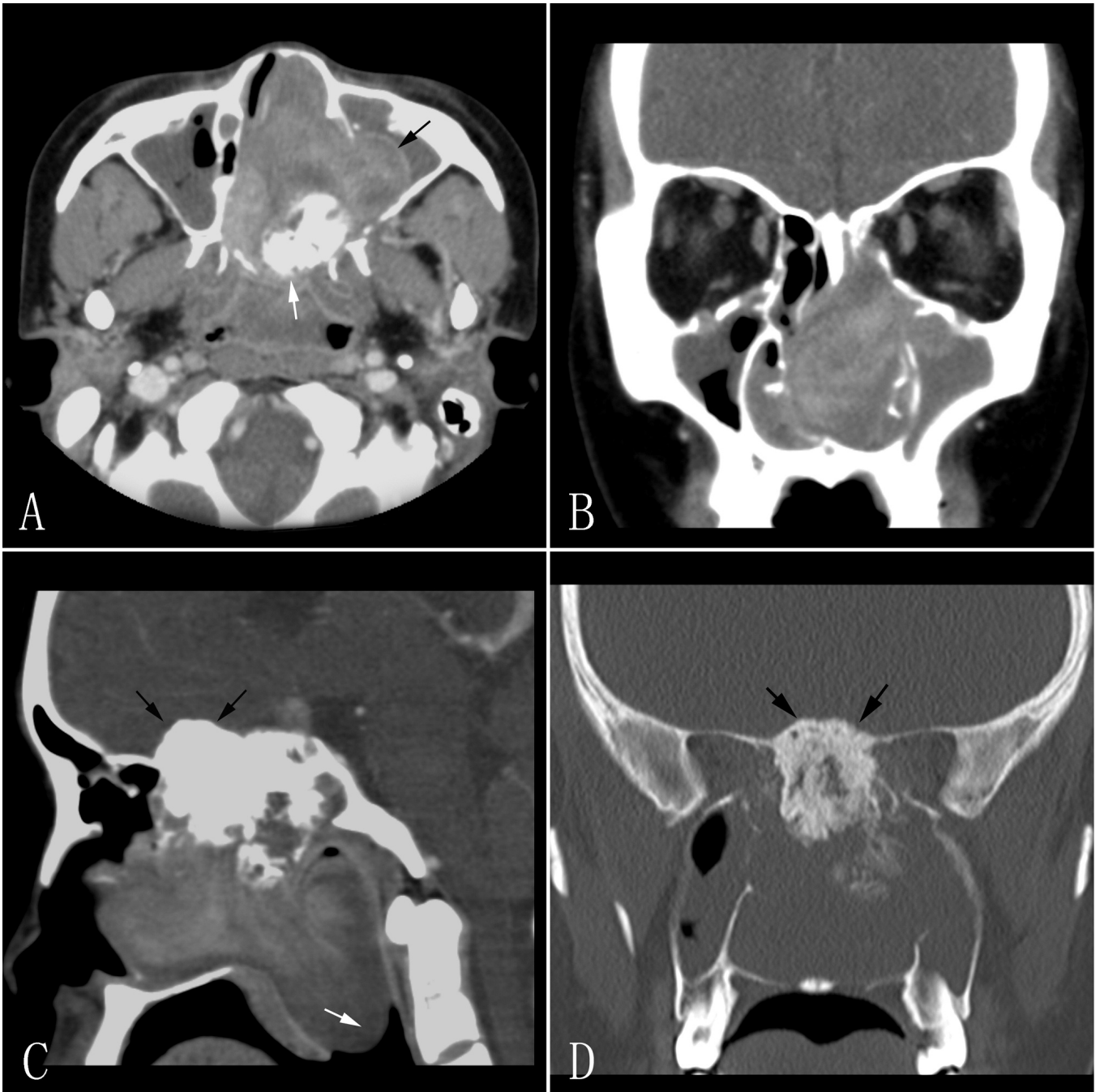
By immunohistochemical staining, the spindle tumor cells showed diffuse immunoreactivity for vimentin, CD99, CD56 and SMA, as well as immunoreactivity for S-100 protein in cartilage (Fig. 3A-D). However, cytokeratin (AE1/AE3), EMA, synaptophysin, NSE, Calponin, desmin, Myo D1, myogenin and Bcl-2 were negative in tumor cells, except that CD34 immunoreactivity was identified in the vascular endothelium. The Ki-67 labeling index of the tumor was variable. In mildly hypercellular areas, the proliferation index was low, up to 1%, but it was very high,

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accounting for 50% in atypical areas of tumor (Fig. 3E). The FISH analysis using a dual color break apart probe within the SS18 gene on 18q11.2 showed no separated

red and green signal in nucleus. There was no t(X;18) translocation found in tumor cells (Fig. 3F).

Based on the pathological findings, the nasal mass



**Fig. 1.** Preoperative radiological findings of the intranasal mass. **A.** Postcontrast axial CT scan in soft tissue windows revealed that a large central area of bulky calcification continuous with hyperostosis at the anterior part of the cribriform plate. An irregular polypoid mass presented in the left nasal cavity displacing the nasal septum. Expansion of left maxillary sinuses (black arrow) and hyperintense foci (white arrow) may be observed in the mass. **B.** Coronal CT scan in soft tissue windows showed that the mass also extended into left ethmoid sinus and eroded the bony margins of the medial wall of the left orbit. **C.** Sagittal CT scan showed mass extended to the floor of the anterior cranial fossa (black arrow) and the posterior portion of the nasal cavity (white arrow). **D.** Coronal CT scan in bone windows showed the cribriform plate was observed to be invaded (black arrow), but mass did not break into the anterior cranial fossa.



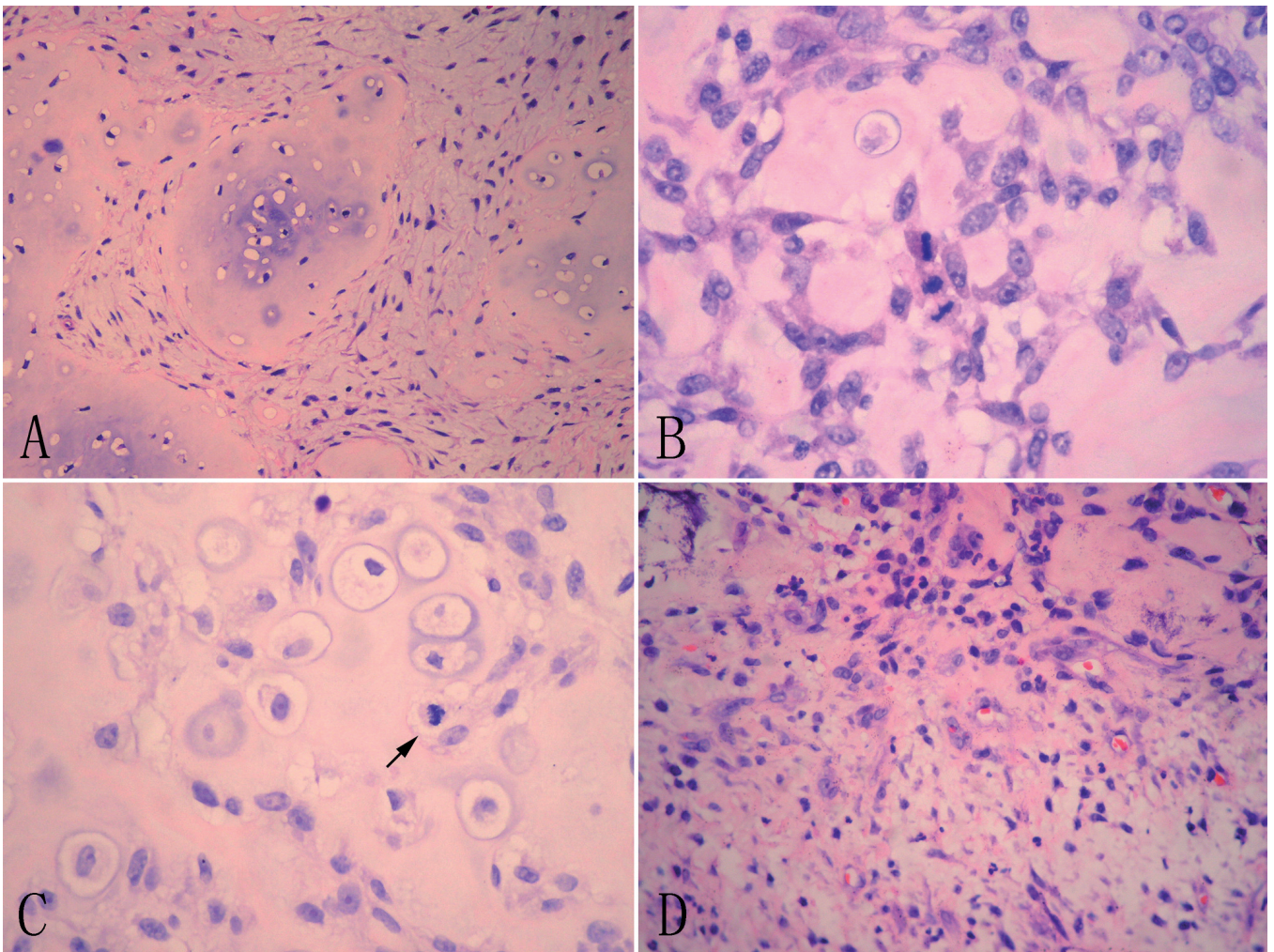
was diagnosed as malignant transformation of nasal chondromesenchymal hamartoma according to WHO diagnostic criteria (Jundt et al., 2005).

### Discussion

The development of NCMH in the region of the nasal cavity and/or paranasal sinuses is extremely rare. However, there is some confusion about the nomenclature of mesenchymal hamartomatous lesions of the nasal cavity because of incomplete understanding of their pathogenesis. Before the term “NCMH” was first used in 1998 by McDermott MB, some cases designated as “chondroid hamartoma (Kim et al., 1999), mesenchymoma (Ludemann et al., 1997) and nasal hamartoma (Terris et al., 1993)” might be the same

lesions in the nasal cavity of neonates. McDermott MB et al. suggested the diagnostic term of NCMH to describe a tumefactive process of the nasal passages and contiguous paranasal sinuses occurring in infancy with similarities to the so-called chest wall hamartoma (McDermott et al., 1998). In 2005, World Health Organization (WHO) classification of tumors of the head and neck accepted NCMH as a new entity of benign tumors of bone and cartilage because of its distinct morphological and clinical characteristics (Jundt et al., 2005).

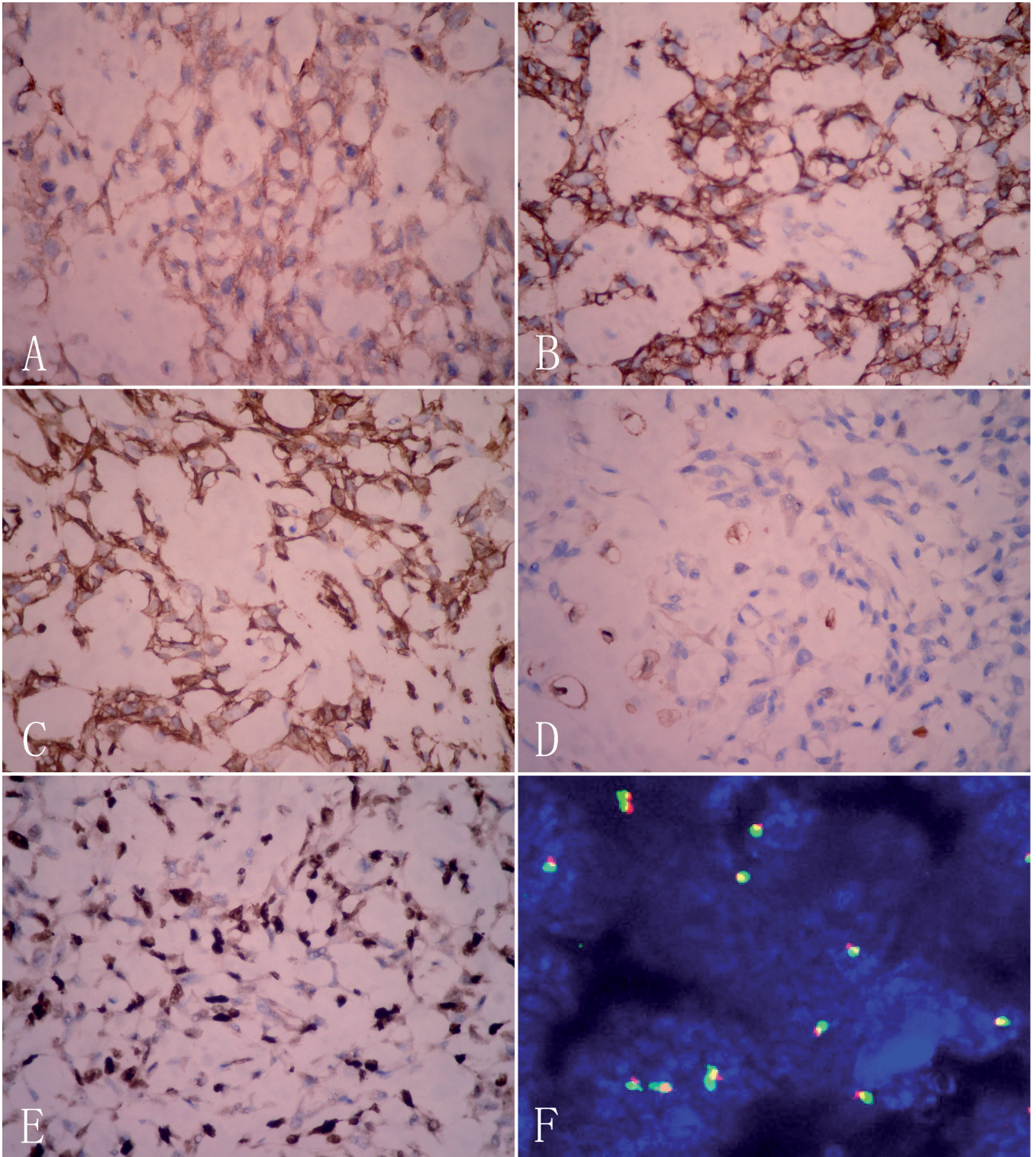
To date, there are 27 bona fide cases reported as NCMH occurring in nasal cavity and paranasal sinuses, including 19 males and 8 females, aged from newborn to 69 years. NCMHs occur predominantly in infants under one year old (14 patients) and children under 15 years



**Fig. 2.** Photomicrographs of the intranasal mass. **A.** In some areas of mass, tumor was composed of irregular islands of mature hyaline cartilage and bland spindle cells, whose morphological features were consistent with typical NCMH. **B.** However, in most areas of tumor, hypercellular spindle cells exhibited cytological atypia with plump nucleus, conspicuous nucleoli and high mitotic activity. **C.** The cartilage islands contained large chondrocytes with conspicuous nucleoli and mitotic figures (black arrow). **D.** The foci of necrosis could be observed in the atypical areas. HE staining, x 400



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**Fig. 3.** Immunohistochemical and cytogenetic analysis of the intranasal mass showed spindle cells were diffusely positive for CD99 (A), CD56 (B), and SMA (C). Immuno-positive signal of S-100 protein was detected in the nucleus of chondrocytes, but not in spindle cells (D). E. Tumor cells showed high Ki-67 index in atypical areas of tumor. F. FISH with break-apart probe for SS18 gene shows one intact yellow signal, indicating the absence of a t(X;18) translocation. A-E, immunohistochemical staining, x 400; F, FISH assay, x 400



old (7 patients). The remaining 7 patients are adolescents and adults, ranged between 16 to 69 years of age. Recent studies have shown that this tumor might be caused by an underlying genetic predisposition in combination with the proper stimulation, because a few cases of NCMH occurring in children are associated with pleuro-pulmonary blastoma and appear to have a cytogenetic aberrance of translocation t(12;17)(q24.1;q21) (El Behery et al., 2012). NCMH typically presents as an intranasal mass but can show aggressive behavior by being an extension of paranasal sinus and cranium through the cribriform plate. The presentation and symptoms depend on the size and location of the tumor, as well as involvement of surrounding structures. Respiratory difficulty and the discovery of an intranasal mass and/or facial swelling are the most common presenting features. Orbital involvement of the tumor can result in ophthalmoplegia, proptosis, ptosis and hypotropia (Kim et al., 2004; Silkiss et al., 2007). Intracranial extension may result in hydrocephalus and oculomotor disturbances (McDermott et al., 1998; Kato et al., 1999; Hsueh et al., 2001; Sarin et al., 2010). In a review of the 27 cases reported in the literature, 29% (8/27) demonstrated intracranial extension, and 18% (5/27) demonstrated orbital extension.

Histologically, all of the reported NCMHs demonstrated a variably cellular fibrous and spindle cell stroma with admixed areas showing predominantly hyaline and well-differentiated cartilaginous nodules. An aneurysmal bone cyst like component or osteoclast-like giant cells could be also observed in some cases (McDermott et al., 1998; Shet et al., 2004). The cytological bland cartilage and mesenchymal cells were observed in all cases. No cases showed atypia of the mesenchymal or cartilaginous cells, and mitotic figures within the mesenchymal component were rare, except for one case showing moderate mitoses (up to 4/10 HPF) without atypical mitoses (Kim et al., 2004). So far, to our knowledge, there have been no reported cases of malignant transformation. However, unlike previously reported cases, the present case was characterized histologically by large and plump nuclei, a distinct nucleolus, and marked mitotic activity (20/10 HPF) in mesenchymal and cartilaginous cells. Histological progression from typical NCMH to atypical areas could be observed in the tumor. The proliferation index was low in typical areas, but very high in atypical areas. Necrosis and atypical mitoses were also detected in the tumor tissues, which were distinct from typical NCMH and coincided with the diagnostic criteria of malignant transformation. To our knowledge, this is the first case of NCMH with malignant transformation. Although NCMH commonly develops in neonate or young infants and exhibits benign histological appearance and favorable prognosis, there is a possibility of malignant transformation in adult patients. Therefore, thorough histological inspection is necessary to accurately diagnose this tumor when it is encountered in adults.

Although several reports indicated that radiological

examination could provide valuable clues in the diagnosis of NCMH (Johnson et al., 2007; Kim et al., 2009; Yao-Lee et al., 2011), in general, the imaging features of this rare tumor are not specific, especially for malignant transformation. Since a malignant morphology appeared in the present case, the hypercellular spindle cell morphology was easily confused with other spindle cell sarcoma containing osseous and cartilaginous components, including mesenchymal chondrosarcomas, chondroblastic osteosarcoma and synovial sarcoma with bone or cartilage metaplasia. In rare conditions, mesenchymal chondrosarcoma may occur in nasal cavity and paranasal sinuses, which typically is composed of an undifferentiated small round cell proliferation and islands of cartilaginous differentiation (Nakashima et al., 2007). Mesenchymal chondrosarcoma shows immunoreactivity for CD99 in undifferentiated round cells and S-100 protein in chondroid areas, which appears to have a similarity to our present case. However, spindle mesenchymal cells, not small round cells, in our case with myofibroblastic differentiation and immunostaining positive for SMA is more supportive of NCMH. A recent study has demonstrated that a novel, recurrent HEY1-NCOA2 fusion appears to be the defining and diagnostic gene fusion in mesenchymal chondrosarcomas, which has not been detected in NCMHs yet (Wang et al., 2012). Chondroblastic osteosarcoma may arise in facial bones and nasal bones. The prominent chondroid matrix of chondroblastic osteosarcoma may readily be mistaken for NCMH. But the diagnosis of osteosarcoma is predicated on the accurate identification of osteoid. The variable thickness of the osteoid in tumor is a distinct histological characteristic to distinguish from NCMHs. Synovial sarcoma occasionally occurs in head and neck with paranasal sinuses or intracranial involvement. Diagnostic complexities arise when monophasic or poorly differentiated synovial sarcoma with bone or cartilage metaplasia is sampled for histological examination. There are sheets of spindle or small round cells with CD99 immuno-positive like those present in our case. However, the t(X; 18) (p11; q11) is the cytogenetic hallmark of synovial sarcoma (Fisher et al., 2007). In the present case, the negative result for fusion SS18-SSX gene detection by FISH assay did not support such a designation.

Previous series of NCMH have described that recurrence is not a feature of NCMH. The patients usually have favorable prognosis when they receive total resection, although residual mass can present silently when the tumor extends into the cranial fossa via cribriform plate (McDermott et al., 1998; Kim et al., 2009). A few cases had been described to apply the radiation and chemotherapy for the lesions that were not completely resected, but the efficacy of treatment was difficult to ascertain (McDermott et al., 1998; Kato et al., 1999). Therefore, some clinicians suggest complete resection is the treatment of choice for this lesion and

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potentially harmful therapies should be avoided (Hsueh et al., 2001; Kim et al., 2009; Sarin et al., 2010). However, in our current case, the demonstration of cytological atypia, marked mitotic activity and necrosis of tumor supported malignant transformation of NCMH. Moreover, rapid tumor recurrence was observed at 3 months after total resection. Postoperative fractionated radiotherapy and chemotherapy, as well as longer period of follow-up should be performed. Regrettably, due to a lack of data in postoperative treatment and follow-up investigation, the prognosis of this patient was uncertain. We postulate that necrosis and high mitotic activity present in the tumor, as well as rapid tumor recurrence will be responsible for a less favorable prognosis for the patient.

In conclusion, we report a rare case of NCMH occurring in an adult patient. In this tumor, some areas show a typical histological characteristic as previously described. However, the other areas exhibit marked malignant appearance, which has not been previously described. To our knowledge, this is the first case of NCMH with malignant transformation. Since there is a possibility of malignant transformation of NCMH in adult patients, a thorough histological inspection and an appropriate immunohistochemical panel, as well as molecular analysis, are essential to accurately diagnose this rare tumor because of potential diagnostic pitfalls. A further case investigation and long period follow-up are necessary to clarify the biological characteristics of NCMH with malignant transformation.

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*Conflict of interest.* The authors declare that they have no conflict of interest.

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