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Clinicopathological features of melanotic and non-melanotic oncocytic lesions of the nasopharynx

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Summary

Oncocytic metaplastic lesions of the nasopharynx are rare benign entities which are divided into melanotic and non-melanotic forms. Less than 40 non-melanotic and 30 melanotic cases have been reported in the literature. We present the largest known case series to date of melanotic oncocytic metaplasia and more than 20 cases of non-melanotic oncocytic metaplasia. Clinical, endoscopic, histological and immunohistochemical features were reviewed. Most cases presented in males starting from their late adulthood. Compared to its non-melanotic counterpart, all cases of melanotic oncocytic metaplasia had a smoking history (p=0.041). All cases of melanotic oncocytic metaplasia were negative to melanocytic markers (S100, HMB-45, Melan-A and MiTF). Although no disease-related mortality was recorded, concurrent melanoma and nasopharyngeal carcinoma were seen in two cases.

Key words: Melanotic oncocytic metasplasia; oncocytic metaplasia; melanin.

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INTRODUCTION

Oncocytic lesions of the nasopharynx are rare but distinct clinical entities. They are classified into melanotic (melanotic oncocytic metaplasia; MOM) and non-melanotic (non-melanotic oncocytic metaplasia; NMOM) forms.[1] NMOM usually presents as an incidental finding on endoscopy,[2] and less commonly local symptoms such as Eustachian tube dysfunction and otitis media.[3] MOM poses a diagnostic challenge as it is a known mimic of melanoma, often presenting as multiple pigmented nodules,[4] but clinically behaves in a benign fashion.[5] To date, less than 40 cases of NMOM[1–3,6] and less than 30 cases of MOM have been reported[5,7] and are mostly limited to single case reports or small case series.

We have reviewed clinicopathological data of cases of oncocytic metaplasia, including MOM and NMOM, and constructed a case series with the largest number of MOM cases reported to date from our institute. In addition, the immunohistochemical (IHC) profile of MOM was reviewed. We aimed to identify clinical associations, prognostic behaviour and diagnostic approach, in terms of light microscopy and IHC, for these lesions.

METHODS

A computerised search of MOM and NMOM in the department's histopathology archives was performed. Archived paraffin-embedded biopsies were recruited for the study. Haematoxylin and eosin (H&E) sections and pathology reports were retrieved and reviewed by the authors.

Several IHC stains that have been proposed to be of diagnostic utility for MOM were reviewed, including melanocytic markers[8] and Masson-Fontana, a melanin stain.[9] Clinical information and endoscopic findings were recorded from each patient's case notes and endoscopy report, respectively. This study was approved by the institute's clinical research ethics committee (Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee, reference number 2018.233, approved 3rd October 2018).

All statistical analyses were performed using the statistical package SPSS, version 23 (IBM, SPSS Statistics, USA). The Fisher's exact test and t-test were used to examine the association between clinical parameters as categorical and continuous variables versus pathological parameters. A p value <0.05 was considered significant.

RESULTS

A total of 33 cases of oncocytic lesions of the nasopharynx, all from individual patients, were diagnosed during the period between January 2000 and December 2018, with nine cases being MOM and 24 NMOM. One case of NMOM and one case of MOM included have been previously reported in the literature.[1]

There was a marked male predilection (male 29/33, female 4/33) with patient age ranging from 31 to 84 years at the time of diagnosis. All cases of MOM had a smoking history. The most common presentation was as an incidental finding (n=17) for screening, investigation or follow-up of other diseases. Local presentations include epistaxis (n=4), nasal obstruction (n=2), rhinorrhoea (n=2), tinnitus (n=2), cranial nerve palsy (n=2), rhinitis (n=1), vertigo (n=1) and hoarseness of voice (n=1) (Table 1). The indication for endoscopy was unavailable in one case. All seven patients with a history of radiotherapy prior to presentation were cases of NMOM. Four cases were associated with other concomitant head and neck pathologies: one (Case 10) nasopharyngeal carcinoma (NPC), one (Case 24) malignant nasal melanoma, and two benign Warthin's tumours (Cases 12 and 15). The average follow-up was 51.1 months. There were eight recorded deaths due to unrelated causes including pneumonia (n=3), respiratory failure (n=1), liver failure (n=1) and metastatic carcinoma (n=3) with no disease-related mortality (Table 1).

Endoscopically, NMOM and MOM presented as unifocal or multifocal lesions. In all but two cases of MOM, pigmentation could be identified on endoscopy. In contrast,

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Table 1 Clinicopathological findings of oncocytic lesions of the nasopharynx

Case	Histology	Sex	Age	Smoking	No. lesions	Alive	Cause of death
1	NMOM	M	80	Smoker	Multiple	No	Pneumonia
2	NMOM	M	53	Non-smoker	Multiple	No	Respiratory failure
3	NMOM	M	60	Unknown	Single	Yes	
4	NMOM	M	60	Smoker	Single	No	Pneumonia
5	NMOM	M	68	Smoker	Single	Yes	
6	NMOM	F	45	Non-smoker	Single	No	Pneumonia
7	MOM	M	57	Smoker	Single	No	Metastatic pancreatic carcinoma
8	NMOM	M	65	Smoker	Single	Yes	
9	NMOM	M	56	Non-smoker	Single	Yes	
10	NMOM	M	38	Smoker	Single	Yes	
11	NMOM	M	31	Non-smoker	Single	Yes	
12	NMOM	M	51	Smoker	Single	Yes	
13	NMOM	F	55	Non-smoker	Multiple	No	Metastatic colorectal carcinoma
14	NMOM	M	84	Smoker	Single	No	Liver failure
15	MOM	M	61	Smoker	Single	Yes	
16	NMOM	M	59	Unknown	Single	Yes	
17	NMOM	M	62	Smoker	Multiple	Yes	
18	NMOM	M	61	Smoker	Multiple	Yes	
19	MOM	M	69	Smoker	Multiple	Yes	
20	NMOM	M	58	Smoker	Single	Yes	
21	MOM	M	56	Smoker	Single	Yes	
22	NMOM	M	68	Smoker	Single	Yes	
23	NMOM	M	81	Smoker	Single	Yes	
24	NMOM	M	66	Non-smoker	Single	Yes	
25	MOM	M	58	Smoker	Single	Yes	
26	MOM	M	52	Smoker	Multiple	Yes	
27	MOM	F	77	Smoker	Single	Yes	
28	NMOM	M	74	Non-smoker	Single	Yes	
29	NMOM	M	71	Smoker	Multiple	No	Metastatic lung carcinoma
30	NMOM	F	70	Non-smoker	Single	Yes	
31	NMOM	M	68	Smoker	Single	Yes	
32	MOM	M	59	Smoker	Single	Yes	
33	MOM	M	59	Smoker	Single	Yes	

MOM, melanotic oncocytic metaplasia; NMOM, non-melanotic oncocytic metaplasia.

only one of the NMOM cases was seen to be pigmented. The lesions appeared as distinctive masses or nodules, mucosal abnormalities including irregularity, congestion or subtle elevation, or normal on endoscopic examination. One case of NMOM presented as a cystic lesion (Table 2).

Histologically, oncocytic lesions appeared as a distinct population of well-formed glandular structures demarcated from a background of benign respiratory-type epithelium, distinguishable at low-power view (Fig. 1A,B). The oncocytic epithelial cells featured an abundant granular eosinophilic cytoplasm and shared similar nuclear morphology compared to the adjacent respiratory-type epithelial cells. Nuclear features were bland with preserved nuclear polarity, smooth and regular nuclear contour, round to oval shape and occasional small distinct nucleoli (Fig. 1C). Mitotic figures were inconspicuous. Cytomorphology of the lesional cells in NMOM and MOM were identical, with the exception of cytoplasmic brown, finely granular and non-refractile melanin pigments seen in MOM (Fig. 1D).

Immunohistochemical studies

The oncocytic epithelial cells in all nine cases of MOM were negative to melanocytic markers including S100 (1:750, EDTA at 98°C for 32 min; Novocastra, NCL-S100p, UK), melanoma antigen (Melan-A, 1:100, EDTA at 98°C for 32 min; Dako, M7196, Denmark), human melanoma black (HMB-45, 1:200, EDTA at 98°C for 30 min; Dako, M0634) and micropthalmia transcription factor (MiTF, 1:20, EDTA at 98°C for 32 min; Dako, M3621) (Fig. 2A–E). S100 stain highlighted dendritic melanocytes interspersed between the oncocytic epithelial cells (Fig. 2B). Masson-Fontana confirmed that the cytoplasmic pigments were melanin in nature (Fig. 2F).

Statistical analysis

Excluding cases with absent clinical data, by comparing MOM and NMOM, a statistically significant association between smoking and the presence of pigmentation was found (p=0.041) by the Fisher's exact test (one-sided) (Table 3). A history of radiotherapy, sex, number of lesions (Table 3) and age did not show statistically significant association with the presence of pigmentation.

DISCUSSION

NMOM was first reported by Morin *et al.* in 1999[2] and MOM by Shek *at al.* in 1995.[10] These cases typically presented as an incidental finding or on investigation for common otolaryngological symptoms. Most of the cases in previous reports, similar to this study, were male and in late adulthood or elderly. Endoscopic appearance of these lesions is highly variable. They can appear as obstructive masses, cysts and nodules, as mucosal abnormalities or as incidental findings in a random screening biopsy. Mass forming lesions can account for the obstructive symptoms, whereas flat lesions are most likely asymptomatic. MOM can resemble melanoma on endoscopy, with the presence of pigmentation and

Table 2 Endoscopic findings of oncocytic lesions of the nasopharynx

Case	Histology	Presenting	Location	Gross pigmentation	Endoscopic findings
1	NMOM	NPC screening (abnormal serology)	Bilateral nasopharynx	Not recorded	Not recorded
2	NMOM	NPC follow-up (post-radiotherapy)	Left nasopharynx	No	Mass
3	NMOM	Unavailable	Nasopharynx	Not recorded	Not recorded
4	NMOM	Parapharyngeal carcinoma follow-up	Left nasopharynx	No	Swelling
5	NMOM	NPC follow-up (post-radiotherapy)	Left nasopharynx	No	Irregular mucosa
6	NMOM	NPC follow-up (post-radiotherapy)	Right nasopharynx	No	Nodule
7	MOM	Nasal obstruction	Right nasopharynx	Yes	Flat lesion
8	NMOM	Rhinorrhoea	Left Eustachian cushion	No	Nodule
9	NMOM	NPC follow-up (post-radiotherapy)	Posterior nasopharynx	No	Irregular mucosa
10	NMOM	Neck mass (NPC)	Left nasopharynx	No	Normal
11	NMOM	NPC screening (abnormal serology)	Right nasopharynx	No	Cyst
12	NMOM	Neck mass (Warthin's tumour)	Right nasopharynx	No	Normal
13	NMOM	NPC follow-up (post-radiotherapy)	Right nasal cavity	No	Mass
14	NMOM	Epistaxis	Posterior nasopharynx	No	Congested mucosa
15	MOM	Neck mass (Warthin's tumour)	Left nasopharynx	No	Mass
16	NMOM	NPC screening (abnormal serology)	Nasopharynx	Not recorded	Not recorded
17	NMOM	NPC screening (abnormal serology)	Bilateral nasopharynx	No	Normal
18	NMOM	Epistaxis	Right nasopharynx and left fossa of Rosenmüller	No	Normal
19	MOM	Rhinorrhoea	Left nasopharynx	Yes	Flat lesion
20	NMOM	NPC follow-up (post-radiotherapy)	Left posterior septum	No	Mass
21	MOM	Epistaxis	Left Eustachian cushion	Yes	Flat lesion
22	NMOM	Epistaxis	Nasopharynx	No	Swelling
23	NMOM	Cranial nerve VI palsy	Right nasopharynx	No	Swelling
24	NMOM	Nasal melanoma follow-up	Nasal septum	Yes	Flat lesion
25	MOM	Cranial nerve VII palsy	Right nasopharynx	Yes	Flat lesion
26	MOM	Tinnitus	Left Eustachian cushion	Yes	Flat lesion
27	MOM	Hoarseness of voice	Left nasopharynx	Yes	Nodule
28	NMOM	Rhinitis	Right middle meatus	No	Mass
29	NMOM	Vertigo	Left nasopharynx	No	Subtle elevation
30	NMOM	NPC screening (abnormal serology)	Central nasopharynx	No	Normal
31	NMOM	NPC follow-up (post-radiotherapy)	Right nasopharynx	No	Normal
32	MOM	Nasal obstruction	Left nasopharynx	Yes	Flat spots
33	MOM	Tinnitus	Left Eustachian cushion	No	Nodule

MOM, melanotic oncocytic metaplasia; NMOM, non-melanotic oncocytic metaplasia; NPC, nasopharyngeal carcinoma.

multifocality which simulates satellite lesions in melanoma.[11] MOMs are usually biopsied regardless of size and elevation due to clinical suspicion of melanoma.[11]

Our study demonstrated an association between smoking and melanin pigmentation in oncocytic lesions of the nasopharynx. In a multicentre case series published in 2004, Sakaki *et al.* first proposed smoking as a predisposing factor for MOM.[12] Subsequent case reports also placed emphasis on the presence of a smoking history.[5,7,8] Similar development of melanin pigmentation with smoking is a reported phenomenon in the skin, lip and gingiva.[13,14] Although the exact mechanism is unknown, multiple theories have been proposed. One theory suggested that nicotine, which shows affinity to intracellular melanin, disturbs the melanin-containing cells, causing the migration of melanosomes and subsequent melanisation.[15] Another animal study concluded that exposure to benzo[a]pyrene, which is present in tobacco smoke and also demonstrates affinity to melanin, results in pigmentation.[16]

Some authors consider oncocytic change attributable to a normal aging process,[11] as most MOM cases are reported in elderly males over 60 years of age. In line with cases in the reported literature, the average age of both NMOM (61.9 years) and MOM (60.9 years) patients exceeded 60 years. In contrast, a history of radiotherapy was only found in NMOM with no cases of MOM reporting radiotherapy exposure. The association of radiation to the development of oncocytic lesions in the head and neck,[17] as well as induction of oncocytic changes in rectal adenocarcinoma,[17] have been reported. It has been proposed that oncocytosis reflects degenerative changes from hypoxia and cytotoxic damage.[18] Even though MOM and MOM share oncocytic features on histological examination, their pathogenesis may be based on entirely different cellular mechanisms.

Although there was no disease-related mortality recorded, there were two cases with malignant pathologies concomitantly diagnosed. In one case, recurrent nasal melanoma was diagnosed in another biopsy adjacent to NMOM. It has been suggested that oral melanosis may precede up to one-third of oral mucosal melanoma.[19] Nonetheless, our case series and previous cases of nasopharyngeal MOM described in the literature reported benign outcomes, without evidence of subsequent malignant transformation. Caution is necessary as the presence of NMOM or MOM does not entirely exclude malignancy, in particular melanoma, and sinister pathologies must be ruled out before attributing gross pigmentation to MOM only.

As opposed the benign nature of NMOM/MOM, nasopharyngeal melanoma (NPM) has a poor prognosis with a 5-year survival rate of 10–30%.[20] Unfortunately, the most common presentations of NPM, namely epistaxis and obstructive symptoms, are shared with NMOM/MOM.[20] NPM can appear as frank polypoid lesions, submucosal lesions or even in amelanotic forms,[20] extensively overlapping with NMOM/MOM. Despite clinical and endoscopic resemblance of NMOM/MOM to NPM, these two entities are

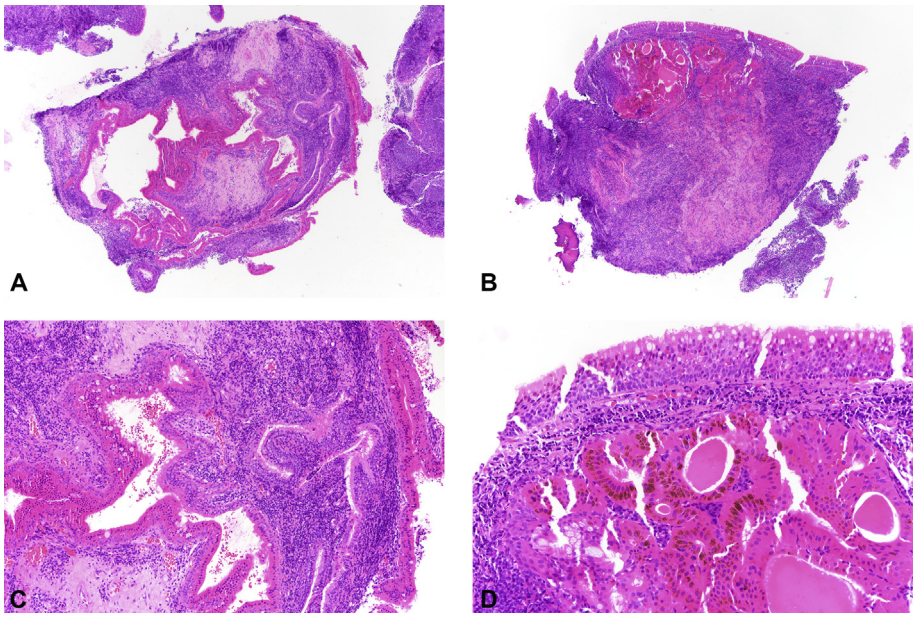

Fig. 1 (A) Non-melanotic oncocytic metaplasia (NMOM) and (B) melanotic oncocytic metaplasia (MOM), low magnification, H&E. (C) NMOM and (D) MOM, medium magnification, H&E.

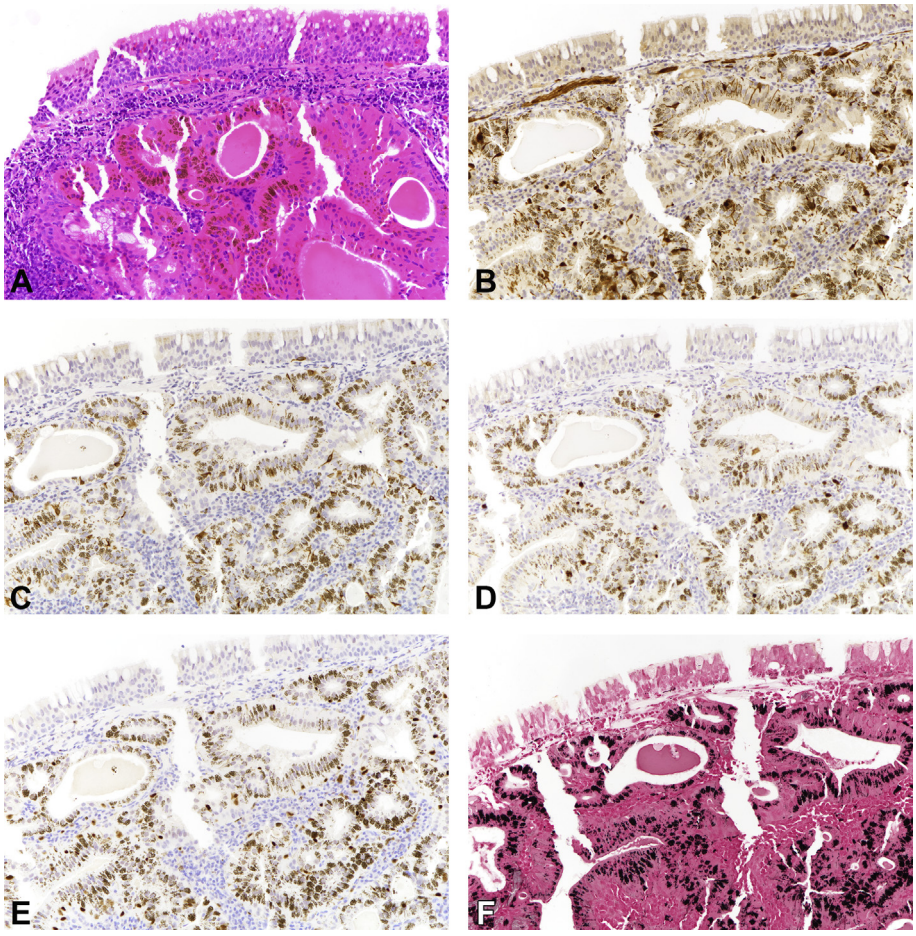

Fig. 2 Melanotic oncocytic metaplasia (MOM). (A) H&E, (B) S100, (C) Melan-A, (D) HMB-45, (E) MiTF, (F) Masson-Fontana, medium magnification.

distinguishable by H&E section and IHC. In our study, all cases of MOM showed benign histological features including preserved glandular architecture and nuclear polarity, bland nuclear features and an absence of mitosis. Histological appearance of melanoma can be highly variable, and oncocytic metaplasia has been reported in melanoma.[21] In case of suspicion, confirmation by IHC is indicated. Melanotic oncocytic epithelial cells are negative to all melanocytic

Table 3 Statistical analysis: Fisher's exact test

	MOM	NMOM	Total	*p* value
Smoking				
Non-smoker	0	8	8	
Smoker	9	14	23	
Total	9	22	31	0.041 (one-sided)
Radiotherapy				
Yes	9	16	25	
No	0	7	7	
Total	9	23	32	0.073 (one-sided)
No. lesions				
Single	7	18	25	
Multiple	2	6	8	
Total	9	24	33	1.000 (two-sided)
Sex				
Female	1	3	4	
Male	8	21	29	
Total	9	24	33	1.000 (two-sided)

MOM, melanotic oncocytic metaplasia; NMOM, non-melanotic oncocytic metaplasia.

markers reviewed in the study, including S100, HMB-45, Melan-A and MiTF.

CONCLUSION

Oncocytic metaplastic lesions of the nasopharynx are benign entities with variable presentation and endoscopic appearance. There appears to be a male predilection to both NMOM and MOM, and melanin pigmentation in MOM is associated with a smoking history. Although MOM may clinically resemble melanoma, MOM can be readily diagnosed by a benign histological appearance and negativity to melanocytic markers. Nevertheless, malignant tumours can coexist with oncocytic metaplasia, and should be ruled out before establishing a diagnosis.

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