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ORIGINAL ARTICLE

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Melanotic oncocytic metaplasia of the nasopharynx: a report of seven cases and review of the literature

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Abstract We describe seven cases of melanotic oncocytic metaplasia of the nasopharynx and review five other cases in the literature. It is usually a small, brown to black lesion that occurs around the Eustachian tube opening, where abundant seromucinous glands and lymphoid tissue are present. Multiple or bilateral lesions are sometimes seen. All 12 reported cases are of Asian origin. Melanotic oncocytic metaplasia occurs predominantly in men (male:female=11:1), with a mean age of 68 years. Simple excisional biopsy appears to be curative. Microscopically, melanotic oncocytic metaplasia is a combination of oncocytic metaplasia of the epithelium of the gland and melanin pigmentation in its cytoplasm. Fontana-Masson staining and immunohistochemical staining of S-100 protein revealed numerous melanocytes with conspicuous dendrites in the glands and stroma, which probably transfer melanin to adjacent glands. The exact pathogenesis of melanotic oncocytic metaplasia is unknown, but we postulate that the lesion could be related to the oncocytic metaplasia of the seromucinous glands around the Eustachian tube, which is followed by the local production and/or acquisition of the melanin pigment, under the influence of certain neuropeptides in the vicinity. The recognition of melanotic oncocytic metaplasia is of clinical importance, as it may be misdiagnosed as a malignancy to the unwary.

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Introduction

Melanotic oncocytic metaplasia of the nasopharynx is a rare lesion, first described by Shek in 1995 [22]. Macroscopically, it is a small, black-pigmented lesion. Coexistence of melanin pigmentation and oncocytic metaplasia in the same gland characterizes the lesion. There have been only five cases reported thus far in the literature [10, 11, 22, 30]. We report seven additional new cases and review the literature with an attempt to elucidate its possible pathogenesis and histogenesis.

Materials and methods

Case selection

Five cases (cases 1–5) were previously reported in the literature, and seven additional new cases (cases 6–12) were retrieved from the files of the Department of Pathology, University of Tokushima School of Medicine, Tokushima, Department of Pathology, University of Hong Kong, Queen Mary Hospital, Hong Kong, and Department of Pathology, Oita Medical University, Oita. Clinical data were obtained from hospital records for the seven cases (Table 1). Hematoxylin–eosin-stained slides from biopsied material were available for the seven cases.

Special staining and immunohistochemical staining

Sections from paraffin blocks of the lesion were used. No sections except hematoxylin–eosin-stained slides were available for cases 10–12. Fontana-Masson staining, Berlin blue staining and immunohistochemical studies for S-100 protein (Dako, Glostrup, Denmark, dilution; 1:500) and HMB 45 (clone, HMB45; Dako, dilution: 1:50) were performed only for cases 6, 7 and 9. For immunohistochemical studies, the sections were bleached prior to standard labeled streptavidin-biotin method with appropriate use of positive and negative controls. Proteolytic predigestion was performed.

Table 1 Clinical findings of five cases in the literature (cases 1–5) and present seven cases (cases 6–12) of melanotic oncocytic metaplasia. *Eustachian O* Eustachian tube opening

Case	Author (year)	Age (years)/sex	Site	Number	Clinical impression	Associated condition	Smoking history
1	Shek et al. (1995) [22]	67/Male	Eustachian O	1	Carcinoma	Otitis media	Unknown
2	Shek et al. (1995) [22]	63/Male	Eustachian O	1	Carcinoma	Tinnitus	Unknown
3	Kurihara & Nakagawa (1997) [11]	69/Male	Left nasopharynx	3	(Incidental)	–	Unknown
4	Hirakawa et al. (1999) [10]	64/Male	Bilateral Eustachian O/ nasopharynx	Multiple	Malignant tumor	Discomfort of the throat	Unknown
5	Xue & Hui (1999) [30]	70/Male	Bilateral Eustachian O	Multiple	Nevus	Tinnitus	Unknown
6	Present case	80/Male	Right nasal cavity/ pharynx	Multiple	Melanoma	Hoarseness, old Tb	10 per day × 50 years
7	Present case	69/Male	Left Eustachian O	1	Melanoma	Rhinorrhea, old Tb	40 per day × 60 years
8	Present case	74/Male	Left suprapharynx	1	Tumor	Epistaxis	Unknown
9	Present case	74/Female	Right Eustachian O	3	Melanoma	Discomfort of the throat	Unknown
10	Present case	68/Male	Nasopharynx	1	Tumor	Increased EBV-IgA titer	Unknown
11	Present case	56/Male	Right Eustachian O	1	Unknown	Hemoptysis	Unknown
12	Present case	63/Male	Left Eustachian O	1	Melanoma	Epistaxis	Unknown

Results

Clinical findings

Clinical findings of 12 cases were summarized in Table 1. The patients were all of Asian origin, and they were comprised of 11 men and only 1 woman, aged 56–80 years (mean, 68 years). All the lesions were a few millimeters in size, brown to black in color and located in the nasopharynx mucosa. They were found near the Eustachian tube opening in 8 of 12 cases. They occurred in the left in 4 cases, in the right in 3 cases and bilaterally in 2 cases. Multiple lesions were seen in 5 cases. Clinicians' impression of the lesion ranged from a malignant tumor, such as melanoma or carcinoma, to a benign melanocytic nevus. Other associated ear, nose and throat symptoms included otitis media, tinnitus, hoarseness of voice, rhinorrhea, epistaxis, discomfort of the throat and hemoptysis. Cases 7 and 8 had the past history of pulmonary tuberculosis. Case 3 had systemic hypertension and was on angiotensin-converting enzyme inhibitor, but the lesion was otherwise asymptomatic. The information about the smoking history was available only for cases 6 and 7: 10 cigarettes per day for 50 years and 40 cigarettes per day for 60 years, respectively. Smoking history for the other patients was unknown. There has been no recurrence or progression of the lesion reported on all these seven cases after biopsy.

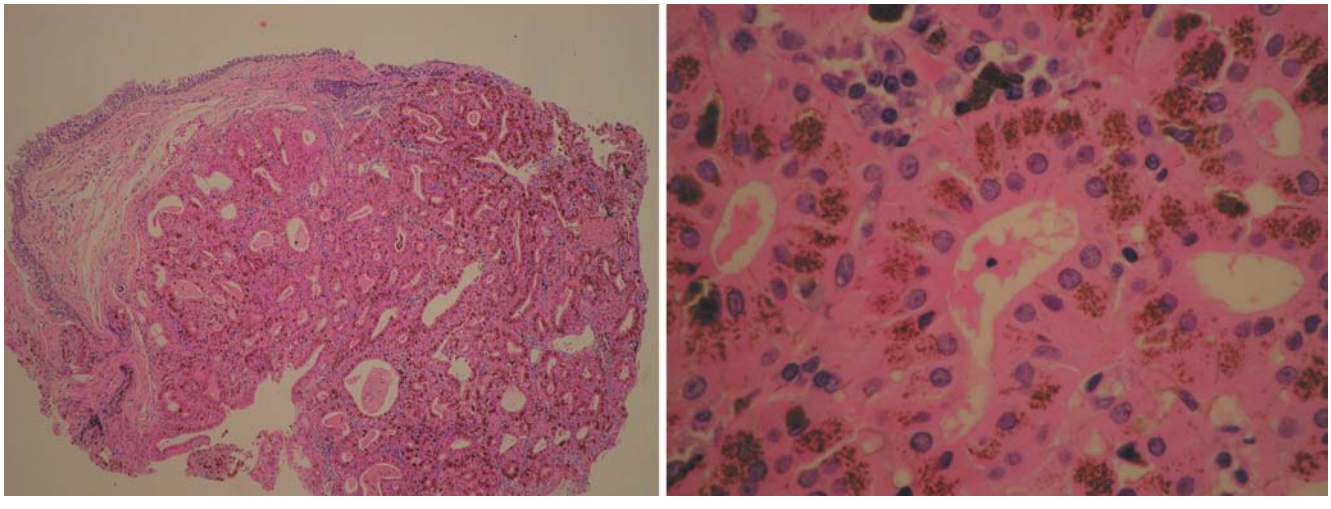

Fig. 1 Beneath overlying respiratory epithelium, a cluster of glands are present (*left*; hematoxylin–eosin, ×15). The epithelium of the glands shows oncocytic metaplasia with melanin pigmentation in its cytoplasm (*right*; hematoxylin–eosin, ×100)

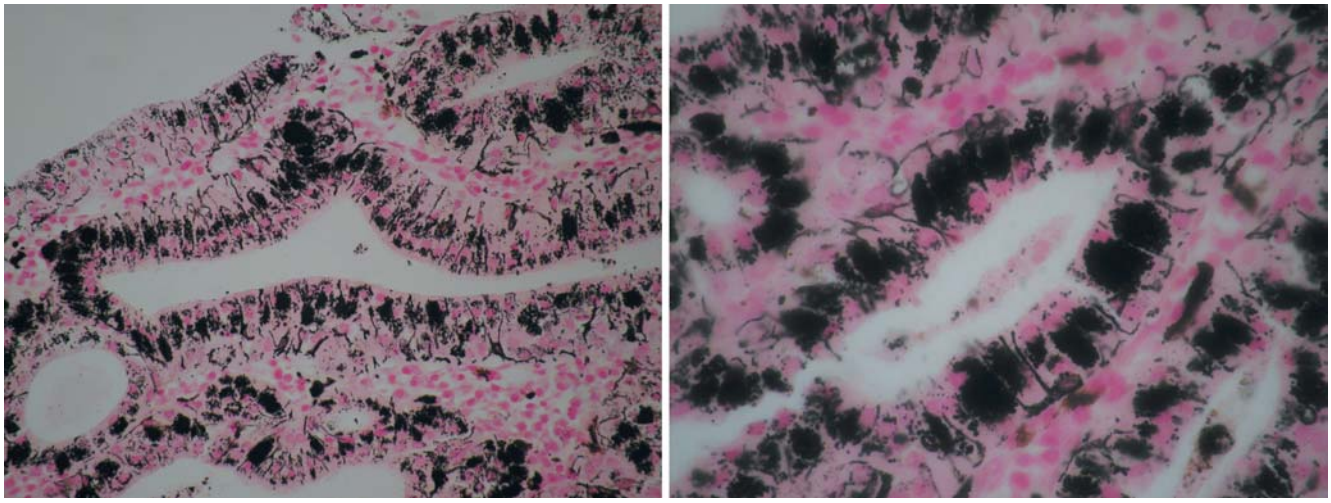

Fig. 2 Fontana-Masson staining reveals numerous melanocytes. Many of them stretch their dendritic processes between the epithelial cells of the glands. (×100, ×200)

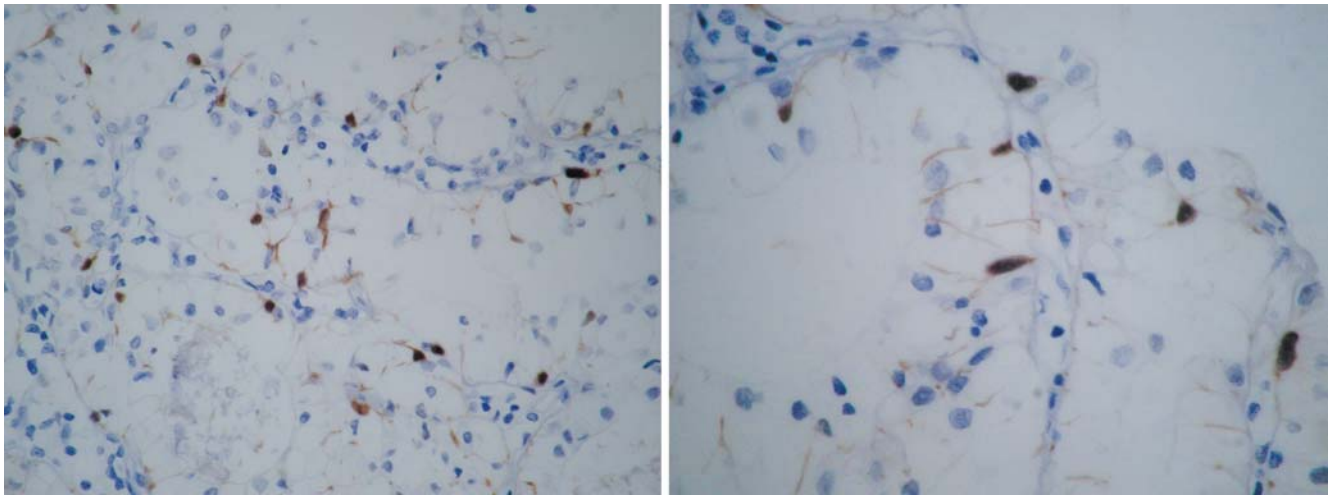

Fig. 3 The location of cells immunoreactive for S-100 protein in the glands corresponds to the one seen in Fontana-Masson staining. (×100, ×200)

Histological findings

Histology of the present seven cases (cases 6–12) was similar. The lesions were well circumscribed, but not encapsulated. Under the overlying respiratory epithelium, which was not present in some cases, there were clusters of seromucinous glands with oncocytic metaplasia and brown pigment in their cytoplasm (Fig. 1). Some glands were dilated and sometimes contained condensed protenacious fluid or melanin granules in the lumina. Pigmentation was also present in the overlying epithelium with or without oncocytic metaplasia. Metaplastic change accompanied the decreased number or absence of mucous cells in the epithelium. No atypia was seen in the epithelial cells of the gland and overlying epithelium. There was scanty amount of stroma between the oncocytic glands, where lymphocytes, plasma cells and some pigmented macrophages were seen. The brown granules stained positive for Fontana-Masson staining and negative for Berlin blue staining, which were indicative of melanin. In Fontana-Masson staining, there were numerous melanocytes with their dendritic processes stretching between the epithelial cells of the glands and abundant melanin granules near them (Fig. 2). Melanocytes were also identified in the surface epithelium and stroma.

Immunohistochemical stainings of HMB 45 and S-100 protein were performed for cases 6, 7 and 9. Dendritic cells were positive for S-100 protein (Fig. 3) and negative for HMB45 in all three cases.

Discussion

The clinical findings on our seven cases and five others in the literature are summarized in Table 1. Melanotic oncocytic metaplasia occurred predominantly in men (1 woman: 11 men) with a mean age of 68 years, and all the patients were Asians. The lesion was usually a few millimeters in size with a slightly elevated surface, and is brown to black in color. Multiple lesions occurred in 5 of 12 (42%) cases and bilateral involvement was sometimes encountered (17%). Most occurred in close vicinity of the Eustachian tube opening (in 8 of 12 cases; 67%). The associated symptoms of tinnitus and otitis media may be caused by compression to the tube [22]. The clinical impression on endoscopic examination is not uncommonly that of a malignant tumor, such as melanoma or nasopharyngeal carcinoma. All the seven present cases pursued a benign clinical course, and no additional treatment is required.

The exact pathogenesis of melanotic oncocytic metaplasia is unknown. Drawing the analogy of the relationship between oral melanin pigmentation and smoking in some races [9, 21, 27], we hypothesize that smoking may be a predisposing factor for melanotic oncocytic metaplasia. The observed male predominance is in keeping with the hypothesis, as there are more male smokers than female smokers among Asians. However, a positive smoking history was only attainable in two patients (cases 6 and 7; Table 1), but was unknown in the other patients. Ethnic background of Asian could be another predisposing factor.

Microscopically, melanotic oncocytic metaplasia is unique in that both oncocytic metaplasia and melanin pigmentation of the epithelium are present simultaneously. Dendritic melanocyte has been reported to exist in the stroma and epithelium of the nasal cavity, paranasal sinus and larynx [7, 25]. In this study, melanocytes were identified in the nasopharynx. Fontana-Masson staining revealed numerous dendritic melanocytes among the epithelial cells of the glands and overlying epithelium and in the stroma in cases 6 and 9 of the present series, and such a finding has been reported in cases 3 and 4 of the previous study [10, 11]. It seems reasonable to postulate that these melanocytes originate in the nasopharynx, since melanocytes are the cells that derived from primordial neural crest and migrate to various sites [1], and that they probably proliferate under the influence of certain trophic substances [22]. The melanin pigment in the oncocytic glands and stroma may be derived from the adjacent melanocytes through their dendrites [10], which is consistent with the observation that ultrastructurally oncocytic cells contained numerous hypertrophied mitochondria, but not premature melanosomes, where melanin is produced [10].

Oncocytic metaplasia of the glandular and ductal epithelium alone is not an uncommon finding, and, in fact, it is considered an age-related phenomenon when seen in the nasopharynx [3, 16], as well as in the salivary gland and larynx [6, 12, 13]. Because it is a more common finding [3, 16] than melanin pigmentation in the nasopharynx, oncocytic metaplasia of the gland probably precedes the melanin pigmentation. The proliferative character of the oncocytes is frequently present in organs with endocrine function or endocrine dependence [8]. In the pharynx and salivary gland, the presence of neuroendocrine peptides has been reported in some species and in humans [2, 4, 14, 17–20, 24, 29, 31]. In addition, it has been shown that some neuropeptidergic nerve fibers located in the tonsil or lymphoid tissue near the tonsil play a regulatory role in the neuro–immuno–endocrine network [5, 23, 26, 28]. Similar lymphoid follicles are also present in the submucosa throughout the nasopharynx, particularly around the Eustachian tube opening, which is sometimes called Gerlach's tonsil [15]. Such neuropeptides might cause the oncocytic metaplasia or melanocyte to proliferate and produce melanin directly or indirectly through the secretion of the oncocytic glands.

In summary, we have described the clinical and histological features of melanotic oncocytic metaplasia. Awareness of melanotic oncocytic metaplasia is of clinical importance, as it may be misdiagnosed as carcinoma or melanoma [10, 22, 30]. Also, because of its histological uniqueness, it is of academic interest and importance to clarify the pathogenesis and histogenesis in further detail.

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