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Abstract

Two cases of malignant melanoma arising in the maxillary sinus are reported. Cytological examination of the solution obtained by local washing through the sinus puncture identified numerous melanoma cells together with melanophages. The cases were then scheduled for well-planned, preoperative treatment. The cytological criteria for diagnosing malignant melanoma are outlined, and the cytological approach is stressed as a valuable diagnostic procedure for early detection of malignant tumors and surveillance of postoperative recurrence, especially in paranasal sinuses.

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PROSPECT OF CYTOLOGIC DIAGNOSIS FOR MALIGNANT MELANOMA IN THE MAXILLARY SINUS

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Abstract. Two cases of malignant melanoma arising in the maxillary sinus are reported. Cytological examination of the solution obtained by local washing through the sinus puncture identified numerous melanoma cells together with melanophages. The cases were then scheduled for well-planned, preoperative treatment. The cytological criteria for diagnosing malignant melanoma are outlined, and the cytological approach is stressed as a valuable diagnostic procedure for early detection of malignant tumors and surveillance of postoperative recurrence, especially in paranasal sinuses.

Key words : malignant melanoma, cytologic diagnosis, maxillary sinus.

Malignant tumor arising primarily from the paranasal sinus often lack clinical signs and symptoms, and thus make early detection difficult. The maxillary sinus is the paranasal cavity with the highest incidence of malignant tumor. Diagnostic techniques such as fiberscopy, x-rays and computerized tomography sometimes fail to detect cancer in early stages thus delaying the time for exploratory opening of the cavity. Even biopsy by exploratory opening often results in a negative diagnosis. In addition, damage of malignant tumor by biopsy should be minimized in order to prevent systemic dissemination. In this respect, preoperative cytological following-up of the patients should be emphasized in the early detection of malignant tumor in the maxillary sinus.

Two cases of malignant melanoma (MM) which were diagnosed cytologically by the examination of specimen washed from the maxillary sinus are reported. The diagnosis in these particular cases made it possible to design a well-planned therapeutic schedule preoperatively. Diagnosis in the cases so far reported were almost always established by histopathologic studies of biopsied materials, while no cases diagnosed cytologically have been reported to date.

REPORT OF CASES

Case 1. The patient was a 53-year-old male, complaining of nasal obstruction and occasional epistaxis for three months. Nasal polyps of little finger-tip

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size were present in the bilateral middle meatus; these were due to chronic sinusitis and were histologically benign. Roentgenologically, there were dense opacities in the left maxillary and ethmoidal sinuses, thinning of the left orbital floor, and a partial bone defect in the lateral wall of the left maxillary sinus (Fig. 1). Other physical and laboratory findings were not contributory.

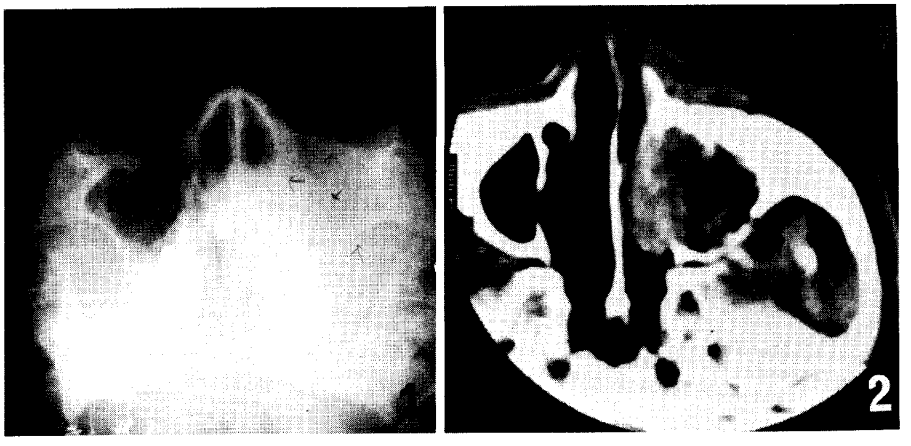

Fig. 1. Occipito-mental view, showing high density in the left maxillary sinus, bone defects in the left orbital floor, the lateral wall of the left maxillary sinus (Case 1).

Fig. 2. Computerized tomography scan, showing abnormal density in the right nasal cavity and maxillary sinus (Case 2): mean density: 35.72.

Case 2. The patient was an 82-year-old male with nasal obstruction for about one month. On the right agger nasi, there was an index finger-tip sized polyp which proved to be a MM by biopsy. X-ray study demonstrated a shadow indicating a tumorous lesion in the right maxillary sinus (Fig. 2). Physical and laboratory findings were not contributory except for mild renal hypofunction and slightly lowered values of immunoglobulin-G, A and M.

MATERIALS AND METHODS

Approximately 0.5 ml lidocain hydrochloride (0.5%) was injected into the inferior meatus for local anesthesia. The maxillary sinus was punctured through the inferior meatus using a Schmidt's needle; resistance in the lateral wall of the inferior meatus was almost absent. The cavity was washed with about 200 ml physiological saline solution. Bloody fluid containing mucosal fragments and coagulated blood mass thus collected was immediately centrifuged for 10 min at 2,000 rpm. Sediment was spread on slide glass, fixed before drying with Cyto Fixer (IATRON) composed mainly of polyethylenglycol and isopropyl alcohol, and stained with Papanicolaou, May-Grünwald-Giemsa and Fontana-Masson for argentaffin reaction.

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CYTOLOGICAL FINDINGS

Case 1. Against a background of a large number of erythrocytes, there were numerous cell clusters; some of clustering cells, *i.e.*, melanoma cells containing fine to coarse melanin pigments (Fig. 3). Isolated melanoma cells were sparse in number compared to the evenly scattered melanophages. The former occasionally contained a large spherical intranuclear vacuole with eosinophilic substance, and very fine intracytoplasmic melanin pigments. The latter engulfed a large number of pigment clumps of uneven size (Fig. 4).

Case 2. Erythrocytes and cell clusters were less pronounced than in Case 1. The most conspicuous finding was marked pleomorphism and multinucleation of melanoma cells. Some of these monstrous cells also contained spherical to oval intranuclear vacuoles (Fig. 5), or internuclear condensation of melanin pigments as pointed out by Hajdu and Hajdu (1). A single melanoma cell sometimes showed mutual inclusion of cells (Fig. 6) as described by Yamada *et al.* (2). Melanin pigments were stained blackish brown against the pink-stained nucleus by Fontana-Masson (Fig. 7) and blue-black by May-Grünwald-Giemsa.

PATHOLOGICAL FINDINGS

As described below in the clinical course and treatment, the materials for the pathology were obtained subsequently to the establishment of cytological diagnosis, *i.e.*, by the time of a partial maxillectomy of the left maxillary sinus in Case 1, and of a radical maxillectomy of the right maxillary sinus in Case 2.

Case 1. Melanoma cells were scattered among wide-spread fibrinoid substance apparently due to hemorrhage and necrosis, and were mostly polygonal and less pleomorphic comparing to Case 2 (Fig. 8). Other areas showed spindle-shaped melanoma cells with rather scant cytoplasm, interlacing in the meshes. Melanoma cells consisted of the round to oval nucleus often with "punched-out" intranuclear vacuoles, and coarse to fine melanin pigments (Fig. 9), which were stained almost black by Fontana-Masson.

Case 2. Interestingly, the respiratory epithelium adjacent to the tumor became completely metaplastic to squamous cell layers; careful search, however, failed to demonstrate junctional activity of tumor cells. Melanoma cells grew expansively and melanin pigments tended to be deposited in somewhat smaller polygonal cells as compared to large pleomorphic cells (Fig. 10). The lesion was dominated by numerous monstrous melanoma cells with round to irregular-shaped intranuclear vacuole, mutual inclusion, prominent nucleolus and sparse intracytoplasmic melanin pigments (Fig. 11).

CLINICAL COURSE AND TREATMENT

Case 1. Subsequent to the establishment of diagnosis, the following thera-

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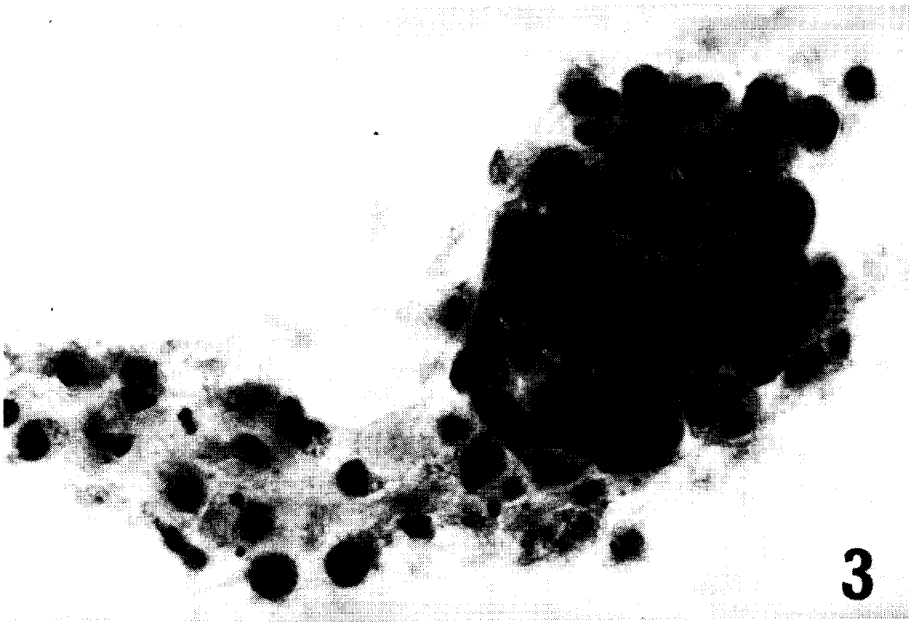


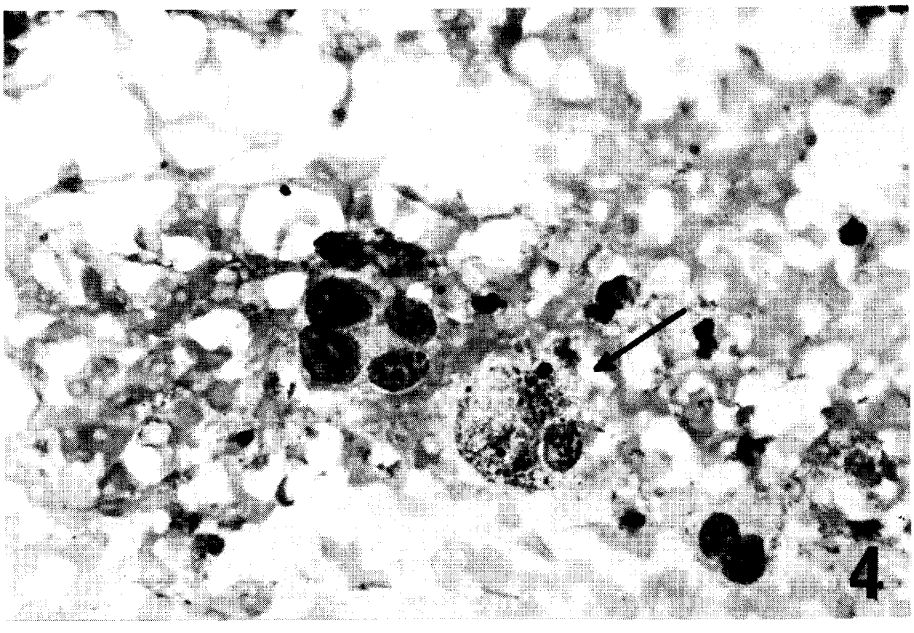
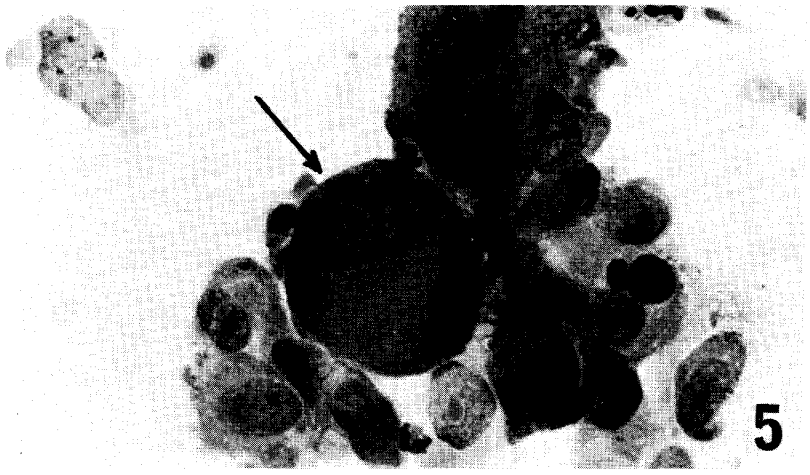
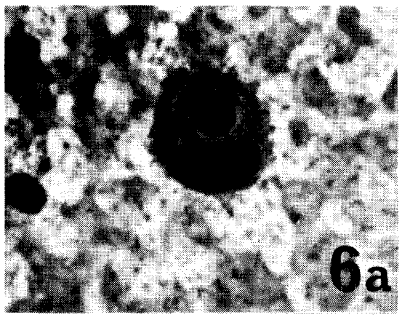
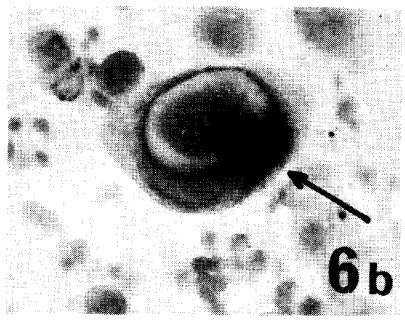


Fig. 3. A tadpole-shaped melanoma cell cluster containing coarse melanin pigments especially in the tail part (Case 1). Papanicolaou, × 400.

Fig. 4. A melanophage (an arrow) phagocytizing various-sized melanin pigments, and multinucleation (Case 1). Papanicolaou, × 400.







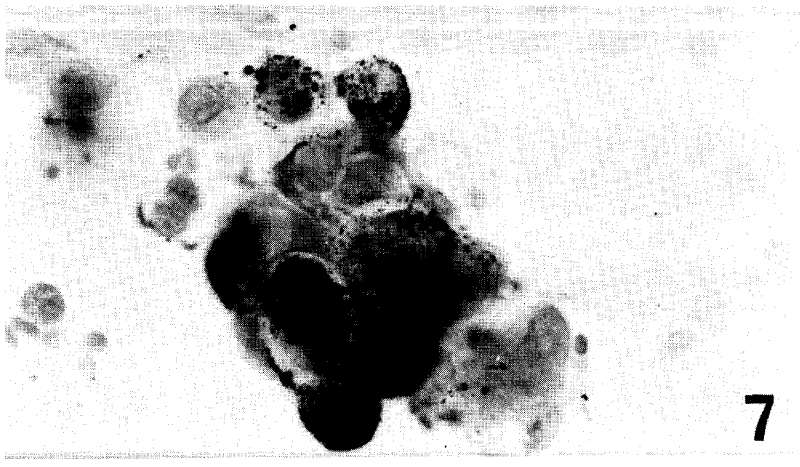


Fig. 5. A few multinucleated melanoma cells with an oval intranuclear vacuole (an arrow) (Case 2). Papanicolaou, × 400.

Fig. 6. A melanoma cell with "mutual inclusion" of cells (Case 2). a: Papanicolaou, × 400. b: showing condensed melanin pigments (an arrow). Fontana-Masson, × 400.

Fig. 7. A melanoma cell cluster with numerous intracytoplasmic melanin pigments (Case 2). Fontana-Masson, × 400.

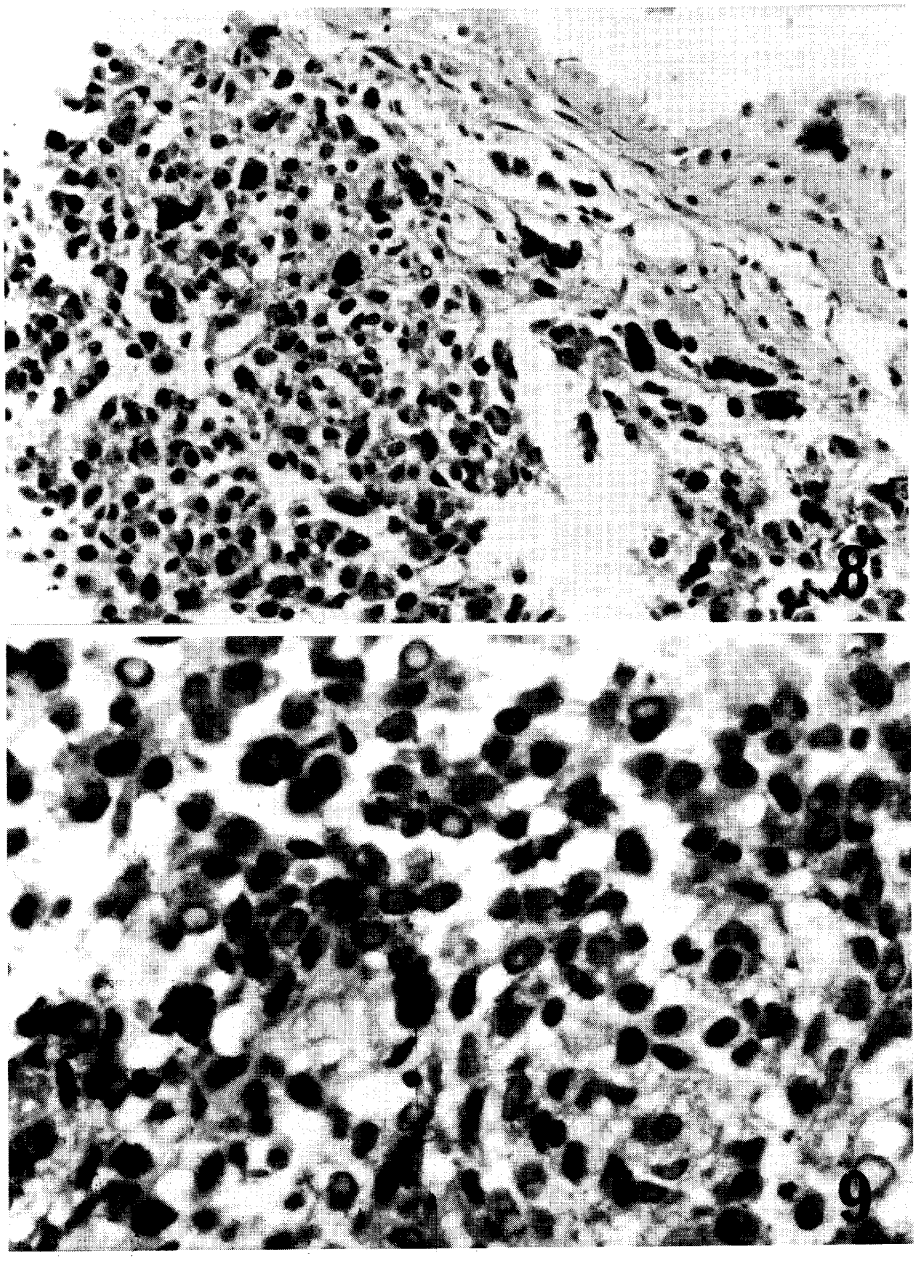
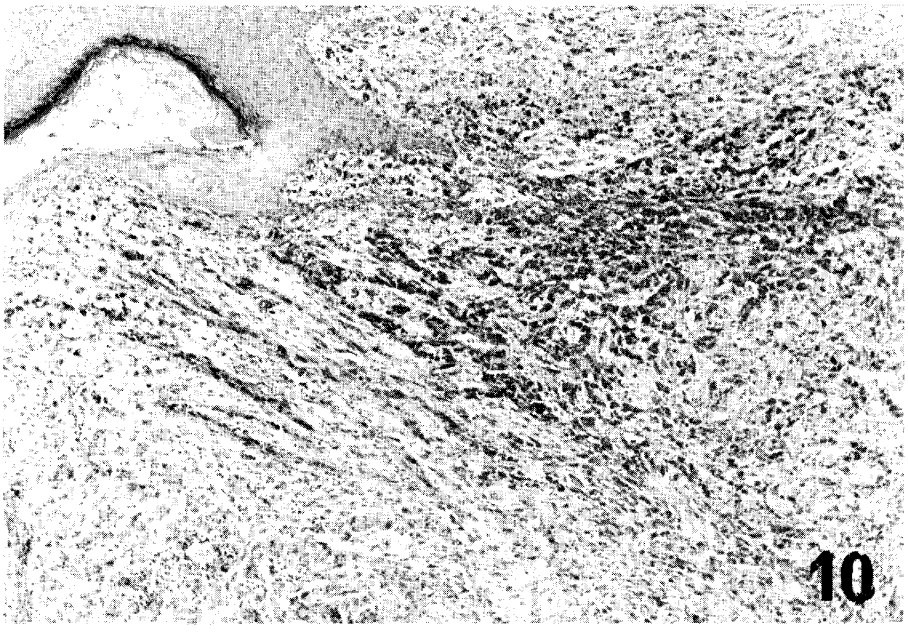


Fig. 8. Malignant melanoma showing the polygonal shape of tumor cells growing beneath the epithelium lining the sinus (Case 1). H.E., × 200.

Fig. 9. Melanoma cells consisting of a round to oval nucleus often with "punched-out" intranuclear vacuoles (Case 1). H.E., × 400.



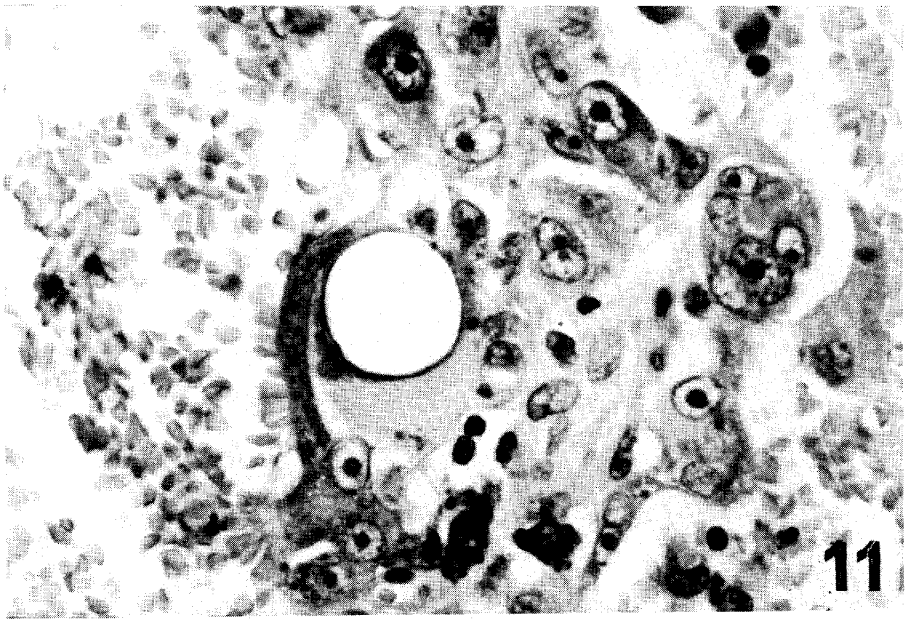


Fig. 10. Malignant melanoma growing expansively beneath the sinus mucosa; note squamous cell metaplasia with keratinization of the epithelium lining the sinus (Case 2). H.E., × 40.

Fig. 11. A melanoma cell in the center with a huge round intranuclear vacuole leaving only the nuclear rim and mutual inclusion, surrounded by numerous melanoma cells with prominent nucleolus (Case 2). H.E., × 400.

pies were commenced: radiotherapy of 3,000 rads with a linear accelerator; and immunotherapies including OK-432 (3, 4) of 2-3 KE semiweekly and intramuscularly, PSK (5) of 3 g per day orally, and BCG (6) of 80 mg once a week and also orally. Afterwards, a partial maxillectomy employing a Weber-Dieffenbach incision was made leaving a part of the hard palate and the posterior wall of the left maxillary sinus, and was followed by prophylactic neck dissection. Several various-sized polyps were seen filling the left maxillary sinus, although the ethmoidal sinus, sphenoidal cells and nasal cavity were free of tumor infiltration. Postoperative recurrence was noted in a part of the maxillary fundus, and cryosurgery was attempted several times. Two years after discontinuation of the immunotherapy, the patient died of disseminated metastasis following intraorbital invasion of MM.

Case 2. After the intranasal polyp was injected once with 100 μg of *Nocardia* cell wall skeleton (7, 8), the right radical maxillectomy was performed. The sinus was almost filled with tumor mass, a part of which protruded into the nasal cavity as a polyp through the middle meatus. Afterwards, 200 μg of *Nocardia* cell wall skeleton in 0.2 ml physiological saline solution was injected intracutaneously seven times, once every week, followed by injections once a month as a maintenance dose. Ten months after surgery, the patient succumbed to enormous hepatomegaly reaching below the umbilicus which appeared to be due to metastasis, although permission for necropsy was not granted.

DISCUSSION

According to a statistical survey between the period from 1961 to 1969 by Seiji and Ohsumi (9), the incidence of MM arising in the mucosa of nose, mouth and pharynx was 7.4, 17.0 and 0.4, respectively, among a total of 501 Japanese subjects. The incidence appears to be increasing recently. Therefore, the possibility of MM in the head and neck must be considered in daily clinical practice. At the same time, as pointed out by Ravid and Esteves (10), diagnosis of the paranasal sinus as the primary origin of MM must be made with caution since it may originate elsewhere such as in the nose, mouth or orbital floor. Another fact to throw doubt upon the paranasal sinus is the primary origin of MM is that the paranasal mucosa often lacks melanocytes. Indeed, according to Shibata (11) who used silver staining on paraffin-embedded sections, only two out of the 21 patients with chronic sinusitis had melanocytes in the paranasal mucosa. Likewise, Holdcraft and Gallagher (12) found no melanocytes in the mucosa of 30 cases not involved by MM. Willis (13) is also reluctant to take the view that "ordinary epidermal cells are incapable of producing melanin and of giving origin to melanomas".

Cytological diagnosis on malignant tumor in otorhinolaryngology was first described by Morrison *et al.* (14) in 1949 and subsequently by Friedmann (15),

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Rubenfeld and Winston (16), Probst and Pfaltz (17) and Sakai (18). Morrison *et al.* (14) maintained that there was high rate of correlation between biopsy and smear; epidermoid carcinoma was reported most often as a tumor diagnosed cytologically, followed by adenocarcinoma and endothelioma. In regard to cytological studies of the maxillary sinus, Fitz-Hugh *et al.* (19) and Okuda *et al.* (20) insisted on its simplicity as a laboratory technique, freedom from surgical intervention and the lack of pain for the patients, easy repetition of the procedure, absence of the risk of disseminating tumor cells, the possibility of detecting tumors throughout the entire cavity, and the high rate of correct diagnosis, *i.e.*, cancer in six among 72 cases studied by Fitz-Hugh *et al.* (19). However, in no cases of MM of the maxillary sinus have cytological techniques using sinus puncture been reported as a diagnostic technique.

The cytological criteria of MM have been described by Yamada *et al.* (2): a) intranuclear vacuolation, occasionally containing an eosinophilic mass; b) finely scattered chromatin; c) unusual nucleolar enlargement; d) faint nuclear membrane; e) mutual inclusion with an epithelioid arrangement; and f) fine melanin granules in the cytoplasm. Hajdu and Savino (21) also emphasized the presence of intranuclear round vacuoli or "inclusions" as a diagnostic aid. Intranuclear vacuoli were remarkable in Case 2 in contrast to Case 1. Generally in tumor cells, intranuclear vacuoli appear as a transient phenomenon during cell degeneration, while the vacuoli of MM develop in cells with no degeneration. Since such vacuolization was described by Apitz (22) in 1937, the pathogenesis of its development has been in dispute, and currently it is believed to be cytoplasmic invagination (21). Yamada *et al.* (2) reported an inverse correlation between the formation of intranuclear vacuoli and the presence of melanin pigments. The nuclear membrane was thin and sharp in both Cases 1 and 2, although the nuclei of Case 2 were more pleomorphic than those of Case 1 and often showed mutual inclusions. These cytological findings resembled those of histopathology.

Melanin granules in the cytoplasm were dark brown and mostly fine in size. Particularly in Case 2, the granules in pleomorphic melanoma cells were difficult to observe microscopically, and needed special staining. In MM of amelanotic type or with sparse melanin pigments, it is almost impossible to detect melanin granules microscopically using only Papanicolaou staining. It is sometimes difficult to distinguish melanin granules from other intracytoplasmic pigments such as hemosiderin and lipofuscin. Melanin pigments then must be indentified with by the tyrosinase activity (23) using DOPA reaction. Another method is the use of Fontana-Masson's argentaffin reaction, in which the silver nitrate-reducing activity of melanin is used and which is feasible to perform and detect melanin pigments as seen in Case 2. When melanin pigments can not be found, it is necessary to differentiate MM from other malignant tumors such as the pleomorphic type of rhabdomyosarcoma, reticulum cell sarcoma, fibro-

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sarcoma or malignant schwannoma. Yamada *et al.* (2), however, stated that the cytological features of the nucleus with a huge nucleolus and the "paradoxical" feature, *i.e.*, with partly epithelial-like and partly nonepithelial-like properties, of the tumor cells in MM were the most reliable criteria for accurate diagnosis of MM.

Cytological approach in the field of otorhinolaryngology has a high diagnostic value for the early detection and screening of malignant tumor as well as of other purulent and allergic diseases of paranasal sinuses. In these lesions, the cytological information is quite useful for deciding on subsequent therapies. In order to collect cellular material more efficiently, improvement in the sampling method, such as techniques for washing the paranasal sinus, are needed. The combined use of other exploratory procedures, *e.g.*, fiberscopy, may also make more accurate diagnosis possible in the future.

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