Primary Malignant Melanoma of the Nasal Cavity

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Malignant melanoma is a highly lethal melanocytic neoplasm, usually affecting the skin. Primary malignant melanoma of the nasal cavity is rarely seen. Clinically, most patients display initial nonspecific symptoms of unilateral nasal obstruction or epistaxis. The prognosis is generally poor, with a mean survival time of 3.5 years. Extensive local invasion and distant metastasis to other organs may occur. The usual treatment of choice is radical excision. Radiotherapy and chemotherapy appear to have little effect. We report a fatal case of intranasal cavity malignant melanoma in which the patient initially presented with blood-tinged sputum, productive cough, and intermittent fever. Preoperative hepatic metastasis was found. Palliative surgery was performed to excise the nasal cavity tumor. Then, 6 courses of chemotherapy were further administered. Unfortunately, regional cervical nodal involvement and pancreatic head metastases occurred 1.5 years after the diagnosis. The patient's condition rapidly deteriorated, followed by death. We have chosen to discuss this aggressive condition because of its rarity and also to emphasize the importance of its early detection through vigilant attention to nonspecific nasal symptoms. A review of the literature concerning intranasal malignant melanoma is presented. We further discuss its possible etiology, site of origin, incidence, clinical presentations, principles of management, and outcome. *(Chang Gung Med J 2003;26:857-62)*

Key words: malignant melanoma, intranasal cavity.

A malignant melanoma affecting the mucosal surfaces of the head and neck is rare. It is even less common when it involves the nasal cavity, accounting for less than 1% of all malignant melanomas.[1] Its clinical features are nonspecific, which frequently cause delays in diagnosis. Prognosis is always poor due to local recurrence, local nodal involvement, and distant organ metastasis occurring months or years after the initial diagnosis. An exceptional case of exclusive liver metastasis without regional lymph node involvement has been reported.[2]

We report on a case of primary intranasal malignant melanoma arising from the left nasal inferior turbinate. Distant metastasis to the liver was found preoperatively. Palliative surgical excision was performed, followed by chemotherapy with dacarbazine (DTIC, demethyl-trizeno-imidazole-carboxamide) and cisplatin. However, metastases to the cervical lymph nodes and pancreas eventually developed 1.5 years after the initial diagnosis. Pathological findings and principles of management are discussed further in this report.

CASE REPORT

A 51-year-old woman was admitted to our hospital in March 1999 due to productive cough, intermittent febrile episodes, and occasional blood-tinged sputum over the course of 3 weeks. The physical examination on admission revealed a blackish nasal mass 2.5×0.5 cm over the left inferior turbinate

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region. Fungal infection was initially suspected. A chest x-ray was unremarkable. Head and neck computed tomography (CT) revealed a left inferior turbinate mass and bilateral acute maxillary and ethmoid sinusitis (Fig. 1A, B). The mass was biopsied. Pathological inspection found the mass to be a pigmented lesion composed of diffusely distributed sheets of neoplastic cells mainly within the submucosal layer (Fig. 2A). The malignant cells had round to oval nuclei with heavily pigmented cytoplasm. A final diagnosis of malignant melanoma was confirmed by immunohistochemical staining for HMB-45, a melanoma marker. Tumor cells were found to be negative for the estrogen receptor. A preoperative

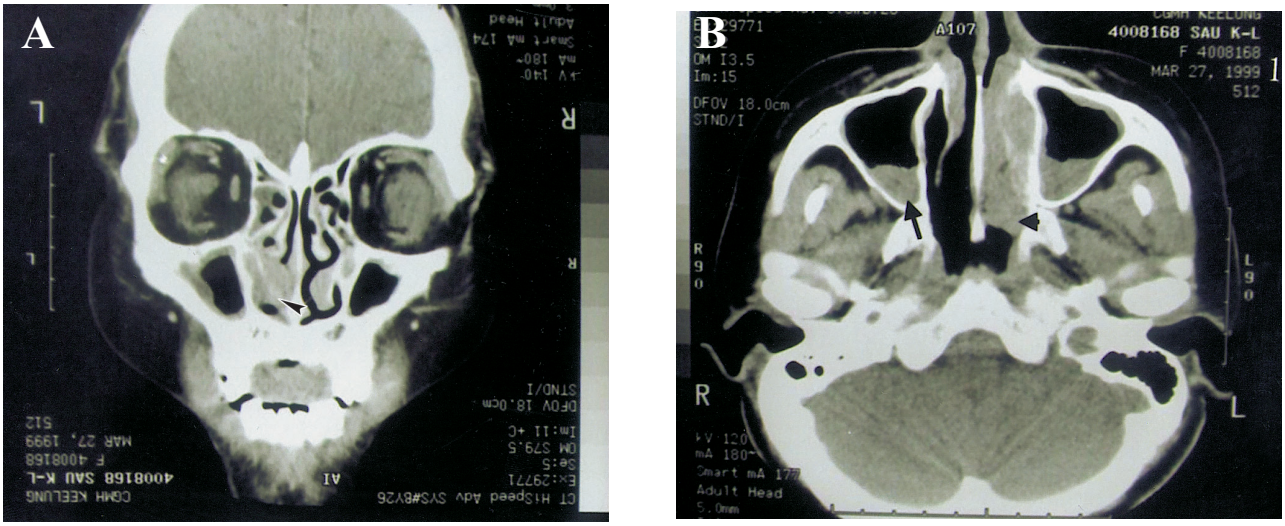

Fig. 1 (A) Computed tomography of the head and neck showing a left-side soft-tissue mass on the inferior turbinate (arrow). Maxillary sinus mucosa thickening and cloudiness of the ethmoid sinuses can also be noted. (B) Computed tomography of head and neck in axial view revealing a left turbinate tumor mass (arrowhead) and the maxillary sinus air-fluid level (arrow), suggesting acute sinusitis.

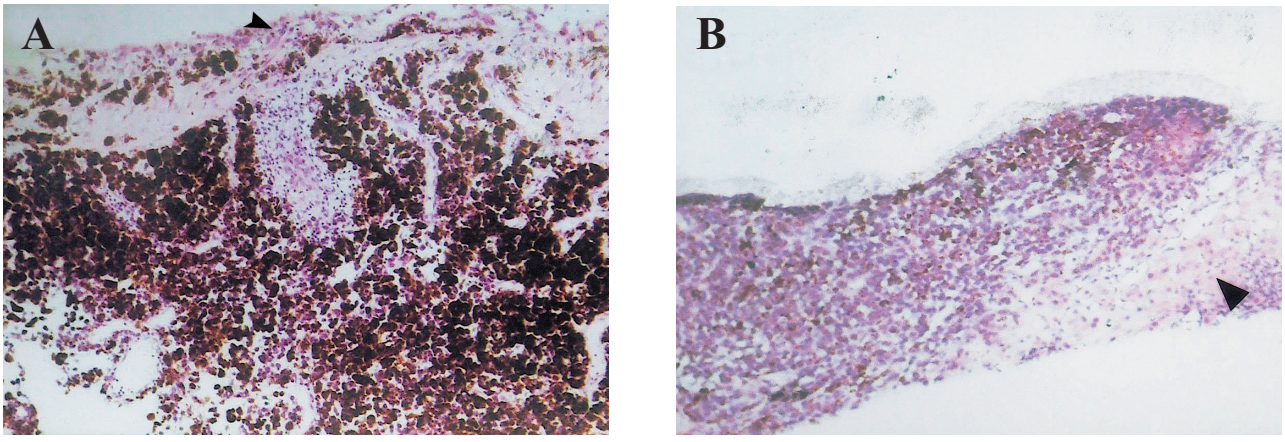

Fig. 2 (A) Photomicrograph showing dense infiltration of neoplastic cells containing abundant brownish melanin pigment within the submucosa of the nasal cavity. The arrowhead indicates the lining epithelia of the nasal cavity. (H&E stain, ×50). (B) A liver biopsy specimen showing the presence of hypercellular metastatic malignant melanocytic cells with heavy pigmentation. The uninvolved liver parenchyma can be seen on the right (arrowhead). (H&E stain, ×50)

bone scan was negative for bony metastasis. Preoperative abdominal echography revealed a hypoechoic nodule measuring 1.4 cm in diameter, located in segment 4 of the liver, which was proven to be a metastatic lesion of the melanoma later by echo-guided liver biopsy (Fig. 2B). Due to intermittent production of blood-tinged nasal discharge and nasal obstruction, palliative surgery with Denker's procedure was performed. During the operation, a black protruding tumor mass, measuring about 2.5 cm in diameter, was seen over the left inferior turbinate. Grossly, the maxillary and ethmoid sinuses were free of tumor. The patient then received 6 courses of chemotherapy with 50 mg/m^2 cisplatin on day 1 and 750 mg/m^2 dacarbazine divided in 3 days on day 1 to 3 at 1-month intervals from December 1999 to August 2000. At the end of the sixth course of chemotherapy, a swollen left neck submandibular nodule was found which progressively enlarged to a size of 6×6×3 cm. The patient complained of neck tightness, pain, and discomfort due to the tumor. Fine-needle aspiration and subsequent excision of the submandibular tumor for relief of her discomfort confirmed the presence of a metastatic melanoma lesion. However, further head and neck CT revealed no local recurrence. A bone scan and liver echogram were also rearranged. The bone scans revealed negative images, while the abdominal echogram showed progressive enlargement of the previously detected liver mass, measuring 2.2 cm in diameter. The patient then received 6 courses of percutaneous injection of ethanol treatment (PIET) for the metastatic liver lesion from October to December 2000.

Later, roughly 3 months after the last course of PIET, the patient complained of diffuse abdominal pain. The abdominal echogram and CT showed 2 pancreatic head masses, measuring 3.4×3.2 cm and 2.7×2.3 cm, respectively. Metastatic lesions were highly suspected but no further pathological verification was made. The patient then received immunotherapy with autologous antigen-loaded dendritic cells which were cocultured with melanoma cells sampled from her left submandibular mass. However, intermittent abdominal pain persisted throughout the hospitalization. In addition, jaundice, peritoneal signs and intermittent febrile episodes developed. Impending respiratory failure occurred, and the patient's condition deteriorated. Finally, the patient was discharged in a critical condition and expired. No autopsy was performed.

DISCUSSION

A primary intranasal cavity melanoma is a rare and usually lethal disease. The exact number of cases and the incidence of the lesion are difficult to assess accurately. Over a 10-year period from 1982 to 1991, the Danish Society for Head and Neck Oncology reported that 34 out of a total of 315 sinonasal cancer patients, or approximately 10.8%, were diagnosed as having an intranasal cavity melanoma.[3] Overall, the incidence of the disease is estimated to range from 0.6% to 3.8%.[4] The incidence in Taiwan remains unknown.

The etiologic and pathologic basis of the disease is not yet fully understood. In 1974, Zak and Lawson reported the presence of dendritic melanocytes in the epithelium of the sinonasal region.[5] In 1979, Cove presented a case of a malignant primary multifocal intranasal melanoma arising from a preexisting nasal and maxillary sinus melanosis.[6] Nevertheless, little is known about premalignant melanocytic lesions in the nose. The role of smoking or sun exposure as an etiology for this tumor remains controversial.[7,8] Holmstrom and Lund reported the occurrence of intranasal melanoma in 3 patients with long-term formalin exposure, however.[9]

In most of the reported series, patients with intranasal melanomas tend to be relatively old being over 50 years at the initial diagnosis. There were no significant gender differences.[4,7,10]

An intranasal melanoma usually manifests as a solitary lesion rather than multiple foci.[7] The anatomic distribution includes the nasal cavity, turbinates, the nasal wall, antrum, ethmoid sinus, vestibules, frontal sinus, and maxillary sinus. Among these locations, the most commonly reported site is the nasal cavity, followed by the maxillary sinus.[7-8,11] In the nasal cavity, the anterior nasal septum, and the middle and inferior turbinates are the most common sites.[12] The precise site of tumor origin is occasionally difficult to identify due to the large size of the tumor and the extensive local destruction it causes.[10]

Clinically, most patients present with symptoms of epistaxis, unilateral nasal obstruction and congestion, and pain and swelling of the cheek and nose.[7,10]

A case of progressive forehead swelling and worsening confusion has also been reported.[11] Yet another case presented with symptoms due to secondary deposits of melanoma in the brain rather than nosebleeds or obstruction.[7] The present case presented with blood-tinged sputum with a persistent, productive cough and intermittent fever, which could have easily been confused with infectious disease or other upper respiratory tract neoplasm.

To establish a diagnosis of primary intranasal malignant melanoma, the pathologist should exclude the presence of a malignant melanoma at other sites, most commonly the cutaneous region. In 1989, Going and Kean presented a primary intranasal melanoma with the presence of melanoma-in-situ of the adjacent mucosa next to the invasive lesion.[13] The finding was considered an unusually well-documented feature found within the primary intranasal melanoma.

Microscopically, most tumor cells appear pigmented. A diagnosis of melanin-rich melanoma is usually not doubtful, nor was it in our case. Melanin pigment deposition can be demonstrated by Fontana-Masson staining.[7] Even so, approximately 50% of cases of this condition show weakly pigmented or even non-pigmented lesions.[14] A case mimicking the appearance of a malignant lymphoma and undifferentiated carcinoma was reported.[2] While immunohistochemical profile staining with anti-S-100 protein, HMB-45, and anti-vimentin can generally confirm the diagnosis,[7] cells occasionally might not be stainable, especially in cases with more spindle-shaped cells. Electron microscopic examination may be helpful in those circumstances. A typical electron microscopic investigation reveals the presence of melanosomes; either in cigar-shaped (type A) or in ovoid- or sphenoid-shaped (type B) forms. The latter has been found to display reluctance to metastasize.[15]

The most fundamental treatment is wide resection of the primary tumor whenever possible. Surgery provides the best chance of controlling the disease.[11] Radiotherapy combined with surgery is recommended in cases of local recurrence or incomplete lesion removal.[10] Optimal radiation doses remain uncertain. Gilligan and Slevin[10] and Thompson et al.[16] suggested high doses of 50-55 Gy in 15 or 16 daily fractions over 21 days. In addition, Thompson et al.[10] also recommended performing simple excision of the involved cervical nodes except in cases when there were simultaneously more than 2 enlarged ipsilateral cervical glands, for which a radical neck dissection was recommended.

In addition, Seo et al.[17] performed chemotherapy in conjunction with administration of the antiestrogen agent, tamoxifen, to treat their 3 patients, and obtained satisfactory responses despite the fact that one of the tumors was unstainable for estrogen receptors. Other chemotherapy regimes, such as those involving Vinca-alkaloids, alkylating agents, and antimetabolites, have been tried, but all yielded disappointing results. DTIC, whose efficacy is still controversial,[12] may be administered as a single agent or in combination with other agents. In our case, the patient was given 6 courses of chemotherapy with DTIC and cisplatin, but metastasis to the neck lymph nodes, liver, and pancreas still occurred after chemotherapy.

In general, such tumors are associated with a poor prognosis and unpredictable course. The prognosis seems unrelated to the size, site, or pigmentation of the tumor. Distant widespread metastases to the liver, lungs, and brain, and regional metastasis to subcutaneous tissues are the major causes of death in most cases.[14] The 5-year survival rate is estimated to be less than 40%.[3-4,7] Loree et al.[18] concluded that head and neck mucosal melanomas, including nasal cavity lesions, and early-stage cases at presentation (i.e., stages I and II) showed more-favorable outcomes (32%) compared to those with stage III or IV (0%) according to the TNM system. Early detection and early diagnosis with appropriate treatment should therefore be emphasized.

In conclusion, it is unclear why the tumor has an unpredictable course and a very poor prognosis. The etiology and pathogenesis remain unknown. Diagnosis by light microscopic examination with hematoxylin and eosin staining may be extremely difficult in amelanotic cases. While chemohormonal therapy with an antiestrogen agent and radical radiotherapy may be helpful, the number of cases is insufficient to draw firm conclusions. Early detection of melanosis and melanoma in-situ lesions may permit possible adequate local control of the primary tumor. We again emphasize that more attention should be paid to patients, especially the elderly, with nonspecific symptoms of unilateral nasal obstruction, blood-tinged sputum, and epistaxis.

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鼻腔原發性惡性黑色素癌

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惡性黑色素癌，是一種致死性之黑色素細胞腫瘤，最常侵犯皮膚。鼻腔原發性黑色素癌極爲罕見。臨床上，多數病患是以單側鼻塞或流鼻血來表現。通常這類原發性惡性黑色素癌預後都不佳，平均存活期爲3年半。這些腫瘤會以局部性侵犯或遠距轉移侵犯其他器官。目前，建議療法是以根除性外科切除法爲主，放射線治療及化學治療的療效則較不明顯。本文報告一位鼻腔內惡性黑色素癌病人，其初始症狀爲血性鼻分泌物，鼻塞，咳痰及間歇性發燒，術前評估疑有肝轉移病灶。病患接受鼻腔腫瘤姑息性療法以解除鼻塞及血性鼻分泌物之症狀後，再接受6次化學治療。然而，化療後仍發生頸部淋巴結、肝臟及胰臟之遠距轉移並致死亡。由於這些罕見的病例並無特殊之臨床症狀，故易造成疏忽或誤診。在此提出本報告案例，藉於提醒臨床醫師，勿忽視任何非特異性之臨床表現，以期能早期診斷，早期治療。本報告亦同時回顧鼻腔內惡性黑色素癌之相關文獻。(長庚醫誌 2003;26:857-62)

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