Malignant melanoma of the nasal cavity: a case report with examination of KIT and platelet derived growth factor receptor-α (PDGFRA)

Tadashi Terada
Departments of Pathology, Shizuoka City Shimizu Hospital, Shizuoka, Japan

Abstract

Although several clinicopathological studies of malignant melanoma of the nasal cavity have been reported, there are no studies of the expression and gene mutation of KIT and platelet derived growth factor receptor-α (PDGFRA) in melanoma of the nasal cavity. A 92-year-old Japanese woman consulted our hospital because of right nasal obstruction and epistaxis. Physical examination and imaging modalities showed a tumor of the right nasal cavity. A biopsy was taken and it showed malignant epithelioid cells with melanin deposition. Immunohistochemically, the tumor was positive for S100 protein, HMB45, p53, Ki-67 (labeling=20%), KIT and PDGFRA. The tumor was negative for cytokeratins (AE1/3 and CAM5.2). A genetic analysis using PCR-direct sequencing revealed no mutation of KIT gene (exons 9, 11, 13, and 17) or the PDGFRA gene (exons 12 and 18). The pathological diagnosis was primary malignant melanoma of the nasal cavity. The tumor was reduced in size by local resection and chemotherapy (Dacarbazine, Carmustine, cisplatine, and tamoxifen), and the patient is now alive and free from metastasis 9 months after the first manifestation. In conclusion, the author reported a case of melanoma of the nasal cavity expressing KIT and PDGFRA without gene mutations of KIT and PDGFRA.

Introduction

Malignant melanoma is a highly malignant tumor, and NRAS and BRAF mutations are mainly involved in the pathogenesis of melanoma.1,2 KIT gene, mapped to 4q12, encodes an oncogenic transmembranous receptor tyrosine kinase, KIT, whose ligand is stem cell factor.3 The platelet derived growth factor receptor-α (PDGFRA) gene, also mapped to 4q12, also encodes an oncogenic transmembranous receptor tyrosine kinase, PDGFRA.4 The KIT gene plays an important role in the melanocyte migration, development, differentiation and tumorigenesis.4 Previous studies have shown that activating mutations of the KIT gene may lead to tumorogenesis of cutaneous melanoma.1 Since KIT and PDGFRA genes are mapped to 4q12, it is anticipated that PDGFRA gene mutations are involved in the tumorogenesis of melanoma, as in the case of gastrointestinal stromal tumors.3 However, PDGFRA gene mutations in melanoma have rarely been examined.5,6 In addition, PDGFRA protein expression has rarely been analyzed in melanoma. These studies have been performed in Caucasians, and only two reports by Ashida et al.4 and ours2 are available in Mongoloids, including Japanese, in which malignant melanoma is much more uncommon than in Caucasians. Ashida et al.4 reported that KIT protein expression was 48% in Japanese cutaneous melanoma and that KIT mutation was 16% in Japanese cutaneous melanoma. Our previous study2 has shown that KIT and PDGFRA expression in cutaneous melanoma was present in 92% and 100%, respectively, and that mutations of KIT and PDGFRA were recognized in 8% and 0%, respectively, in cutaneous melanoma. Although several clinicopathological studies on melanoma of the nasal cavity have been performed2,10 there have been no studies of KIT and PDGFRA in melanoma of the nasal cavity. In the present study, the author investigated the protein expression and gene mutation status of KIT and PDGFRA in a case of nasal melanoma of a Japanese woman.

Case Report

A 92-year-old Japanese woman consulted our hospital because of right nasal obstruction and epistaxis. Physical examination revealed a black tumor measuring of the right nasal cavity (Figure 1). A biopsy was taken, and the biopsy showed malignant epithelioid cells with brown pigment deposition (Figure 2). The brown pigment was positive with Fontana-Masson stain, and thought to be melanin.

An immunohistochemical analysis was performed, using Dako’s Envision method, as previously described.4,11 Immunohistochemically, the tumor cells were positive for S100 protein (Figure 3), HMB45 (Figure 4), p53, Ki-67 (labeling=20%), KIT (Figure 5) and PDGFRA (Figure 6). The tumor was negative for cytokeratins (AE1/3 and CAM5.2).

Genetic analyses of the KIT gene (exons 9, 11, 13, and 17) and the PDGFRA (exons 12 and 18) gene were performed by the PCR direct sequencing method, as previously reported.13-17 The exons of both genes were selected because

Figure 1. Computed tomography demonstrate obstructing tumor in the right nasal cavity: A) frontal section; B) coronal section.
they are frequent mutation sites. The primers are shown in Table 1. In brief, genomic DNA was extracted from paraffin blocks with proteinase K digestion and phenol/chloroform extraction, and subjected to PCR for 40 cycles (94°C for one minute, 52°C for one minute, 72°C for one minute), using a thermal cycler (GeneAmp PCR system 9700, Applied Biosystems, ABI, CA). The annealing temperature was 53°C. PCR products were extracted, and subjected to a computed automatic DNA sequencer (ABI PRISM 3100 Genetic Analyzer, Applied Biosystems, ABI, CA). These techniques revealed that there were no mutations of the KIT gene (exons 9, 11, 13, and 17) or PDGFRA gene (exons 12 and 18) in this tumor. The pathological diagnosis was primary nasal melanoma. The tumor was resected as far as possible by operation. The tumor was reduced in size by the operation and chemotherapy (Dartmose regimen: dacarbazine, carmustine, cisplatine, and tamoxifen). Five courses of Dartmouth regimen were performed. Extensive operation, lymph node dissection and radiation therapy were not performed because of the patient’s old age (92 years). The patient is now alive free from metastasis 9 months after the first manifestation.

Table 1. Primer sequence

|                | Forward                          | Reverse                          |
|----------------|----------------------------------|----------------------------------|
| **KIT exon 9** | 5'-TCC TAG AGT AGG CCA GGG CTT-3' | 5'-TGG TAG ACA GAG CCT AAA CAT OC-3' |
| **KIT exon 11**| 5'-GAT CTA TTT TCC CCT TTC TC-3' | 5'-AGC CCC TGT TTC ATA CTG AC-3' |
| **KIT exon 13**| 5'-GCT TGA CAT CAG TTT GCC AG-3' | 5'-AAA GGC AGC TGG GAC ACG GCT TTA-3' |
| **KIT exon 17**| 5'-CTC CTC CAA CCT AGT GT-3'    | 5'-GTC AAG CAG AGA ATG GGT AC-3' |
| **PDGFRA exon 12** | 5'-TTG GAT CAT CAG TTA CCT GTC-3' | 5'-CAA GGG AAA AGC TCT TGG-3' |
| **PDGFRA exon 18** | 5'-ACC ATG GAT CAG CCA GTC TT-3' | 5'-TGA ACG AGG ATG AGC CTG ACC-3' |

Discussion

The present study is the second report of PDGFRA protein status in melanoma and is the first in melanoma of the nasal cavity. Our previous study showed 100% expression of PDGFRA protein in cutaneous melanoma. The present study is the forth report of PDGFRA mutations in melanoma; the first was reported by Curtin et al., who found no PDGFRA mutations in 26 cutaneous melanomas. The second was reported by Sihto et al., who demonstrated no PDGFRA gene mutations in 14 cutaneous melanomas. The third was reported by Willmore-Payne et al., who showed only 2% of melanomas had KIT mutations. Sihto et al. showed no KIT mutation in 14 cutaneous melanomas. In contrast, Curtin et al. showed that KIT mutations are present in 39% of mucosal melanomas, in 36% of acral melanomas, 28% in melanomas of sun-damaged skin, and in 0% of melanomas of non-sun-damaged skin. Beadling et al. recently reported that KIT mutations were present in 23% of acral melanomas, 15.6% of mucosal melanomas, 1.7% of cutaneous melanomas, 7.7% of conjunctival melanomas, and 0% of choroidal melanomas. Handolias et al. reported that KIT mutation was present in 2% of melanomas and that KIT mutation is frequent in acral and sun-damaged skin melanomas and mucosal melanomas while it was very rare in non-sun-damaged skin melanoma. In the present case,
no mutations were seen in the KIT gene. Since KIT mutational studies are scant in nasal melanoma, more studies remain to be performed.

The present case showed positive KIT protein expression in nasal melanoma. The percentage of KIT expression in cutaneous melanomas varies among researchers. There have been no reports of KIT expression in nasal melanoma, to the best of our knowledge. The percentage in the literature ranges from 21% to 84%. Sihto et al. reported that KIT expression in most human solid tumors, including melanomas, were due to KIT gene amplification. More studies of the relationship between KIT gene mutations and KIT protein expression in nasal melanoma remain to be performed.

In conclusion, the author reported a case of melanoma of the nasal cavity expressing KIT and PDGFRA proteins without gene mutations of KIT and PDGFRA.

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