Lacrimal Sac Malignant Melanoma in 15 Japanese Patients: Case Report and Literature Review

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Abstract

Background. Primary malignant melanoma of the lacrimal sac is rare. A patient with lacrimal sac melanoma was presented, and 14 Japanese patients with lacrimal sac melanoma in the literature were reviewed. Case Presentation. A 78-year-old Japanese man was presented with painless swelling of the lacrimal sac on the left side. Dacryocystectomy revealed diffuse infiltration with large epithelioid cells, sometimes with pigments, which were positive for cocktail mix of antibodies to tyrosinase, melan A (MART-1), and HMB45, leading to pathological diagnosis of melanoma. One month later, positron emission tomography (PET) revealed 2 high-uptake sites (SUV\textsubscript{max} = 10.29 and 15.38) at the levels of medial canthus and nasolacrimal duct, but no abnormal uptake in the other site of the body. The lesion had the BRAF V600E mutation. He began to take daily oral dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor), leading to no abnormal uptake on PET in half a year. He had stable disease in good physical status with small and weak uptake sites of lymph nodes on PET 1 year later. Results. In the review of 15 Japanese patients, including this patient, local recurrence was noted in 4 patients, regional lymph node metastasis only in 3, distant metastasis in 6, and no metastasis in 6. Five patients died within 2 years and the others were alive in short follow-up periods. Conclusions. Chemotherapy was the standard for local recurrence or metastasis. Emerging molecular target drugs, as shown in the present patient, would change the strategy for management of lacrimal sac melanoma.

Keywords
lacrimal sac, malignant melanoma, BRAF inhibitor, dabrafenib, MEK inhibitor, trametinib, BRAF mutation, PET/CT

Background

The lacrimal sac is a component of the ocular adnexa in the orbit and serves as a drainage system of the lacrimal fluid from the ocular surface through the nasolacrimal duct to the nasal cavity. The benign and malignant neoplasms arising in the lacrimal sac have been reported collectively as orbital tumors. Epithelium-derived neoplasms and lymphomas are dominant among basically rare tumors in the lacrimal sac. Malignant melanoma arising in the lacrimal sac is extremely rare, and a limited number of case reports in the literature can be listed on hand. In this study, we present a Japanese patient with lacrimal sac melanoma who underwent a modern combination therapy of molecular target drugs, dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor). We also reviewed 15 Japanese patients with lacrimal sac melanoma, including the present patient, who were described in the literature.

Case Report

A 78-year-old man was presented with 10-month history of waxing and waning painless swelling of the lacrimal sac on the left side (Figure 1E). The pigmentation was noted on the lacrimal caruncle on the left side (Figure 1H). The best-corrected visual acuity was 1.0 in the right eye and 0.9 in the left eye. The ocular media and fundi in both eyes were normal. He had undergone total gastrectomy for stomach cancer 8 years before the onset of the current symptoms. The lesion covered the lacrimal fossa and anterior lacrimal crest, and the partial dacryocystectomy was performed to alleviate pain and swelling. The histopathological examination revealed diffuse infiltration with large epithelioid cells, sometimes with pigments, which were positive for cocktail mix of antibodies to tyrosinase, melan A (MART-1), and HMB45, leading to pathological diagnosis of melanoma. The lesion had the BRAF V600E mutation. He began to take daily oral dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor), leading to no abnormal uptake on PET in half a year. He had stable disease in good physical status with small and weak uptake sites of lymph nodes on PET 1 year later.

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previously and endoscopic colon polypectomy 4 months previously. His medication was daily amlodipine 5 mg only. Computed tomographic scan showed a 1-cm-sized round homogeneous mass with no bony change on the left lacrimal fossa (Figure 1A). He underwent left lacrimal sac tumor extirpation under general anesthesia. The lacrimal sac filled with black mass was carefully separated from the surrounding tissue, and pigmented epithelial lesions along the nasolacrimal duct were removed as deep as possible into the duct.

The pathological examination showed malignant melanoma. The entire lacrimal sac was infiltrated with large epithelioid cells with anomalous nuclei, sometimes, multinucleated large cells in a diffuse pattern (Figure 2A and B). Pigmented abnormal cells were also present in foci. Infiltrating cells were positive for cocktail-mix antibodies against tyrosinase, melan A (MART-1, melanoma antigen recognized by T cells-1), and HMB45 (Figure 2D), but negative for cytokeratin AE1/AE3 (Figure 2C) or CAM5.2. A cluster of small lymphocytes were noted among the large neoplastic cells (Figure 2B).

One month later, he developed subcutaneous pigmented bumpy lesions surrounding the medial canthus (Figure 1F), and whole-body 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography fused with computed tomography (PET/CT) showed 2 high-uptake sites at the levels of medial canthus ($SUV_{\text{max}} = 10.29$, B) and nasolacrimal duct ($SUV_{\text{max}} = 15.38$, C). About half a year after oral dabrafenib (Tafinlar) 300 mg daily plus trametinib (Mekinist) 2 mg daily, the subcutaneous lesions subsided (G) with unchanged conjunctival pigmentation on the lacrimal caruncle (H) and no abnormal uptake on PET/CT (D).

Figure 1. Lacrimal sac mass (E) on the left side on computed tomographic scan (A) at the initial presentation in a 78-year-old man. About 1 month after dacryocystectomy, subcutaneous pigmented lesions (F) were noted and whole-body 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography fused with computed tomography (PET/CT) showed 2 high-uptake sites at the levels of medial canthus ($SUV_{\text{max}} = 10.29$, B) and nasolacrimal duct ($SUV_{\text{max}} = 15.38$, C). About half a year after oral dabrafenib (Tafinlar) 300 mg daily plus trametinib (Mekinist) 2 mg daily, the subcutaneous lesions subsided (G) with unchanged conjunctival pigmentation on the lacrimal caruncle (H) and no abnormal uptake on PET/CT (D).
medications at the same doses. No adverse event, except for occasional mild nausea, was noted throughout the course.

**Methods**

To analyze historical cases from the literature, the Japanese literature was searched for the key words “lacrimal sac malignoma (in Japanese)” in Igaku Chuo Zasshi (Japana Centra Revuo Medicina). Old literatures were further collected from references cited in the articles identified during the literature search. PubMed was also searched for the key words “lacrimal sac melanoma.”

**Results**

The 15 Japanese patients with lacrimal sac malignant melanoma, including the present patient, were 7 men and 8 women, with the age at the initial presentation ranging from 41 to 80 (median = 60) years (Table 1). The tumor was present on the right side in 6 patients, and on the left side in 8 patients, with unknown laterality in 1 patient (Case 9). Local recurrence was noted in 4 patients including the present case, regional lymph node metastasis only in 3 patients, distant metastasis in 6 patients, and no metastasis in 6 patients. As an initial surgery, all 15 patients underwent dacryocystectomy, except for 1 patient with orbital exenteration (Case 5). Lymph node dissection was done in 3 patients. Chemotherapy as a standard regimen at that time, including dacarbazine alone or combination of dacarbazine and nimustine, or further combined with vincristine or carboplatin was done in 7 patients. Additional surgeries for local recurrence were done in 2 patients. Local radiotherapy was applied to metastatic lesions, including the brain, in 2 patients. Two patients had both local recurrence and metastasis. Five patients died within 2 years and the others were alive although the follow-up periods were short. Pathologically, all patients showed epithelioid-type melanoma cells, except for one (Case 8) with spindle cell melanoma.

**Discussion**

The present patient showed local recurrence of malignant melanoma along the nasolacrimal duct in addition to the subcutaneous infiltration. The recurrent melanoma was unresectable, and thus, a combined therapy with oral dabrafenib and trametinib was applicable since the tumor had the BRAF mutation. The patient maintained the stable disease with no local recurrence but with small...
lymphadenopathy later in one and a half year after the initial surgery of dacryocystectomy. He was in good quality of life and had only tolerable adverse event as mild nausea. In the development of distant lymphadenopathy with mild abnormal uptake on PET/CT, we decided to continue dabrafenib and trametinib and not to switch to PD-1 or PD-L1 antibodies because PD-1 or PD-L1 antibodies might cause adverse event, resulting in poor quality of life. It should be noted that foci of infiltration with small lymphocytes were present among the large melanoma cells. This fact suggests that PD-1 or PD-L1 antibodies might work in recovering the immune surveillance to neoplastic cells.

In literature review of Japanese patients with lacrimal sac melanoma, only 14 patients were found as case reports. The main features of lacrimal sac melanoma in 15 patients, including the present patient, were no dominance in gender and laterality. One third of patients had neither local recurrence nor distant metastasis after the initial surgery of dacryocystectomy. The patients with lymphadenopathy or distant metastasis or their combination usually underwent systemic chemotherapy based on dacarbazine and nimustine at that time, but died within 2 years after the initial surgery. Therefore, the prognosis was basically poor when metastasis was present.

In the emerging trend with new therapeutic drugs, BRAF inhibitor and MEK inhibitor, the strategy for management of lacrimal sac melanoma would be drastically changing. As complete as possible extirpation of the lacrimal sac remains the basis for local control and pathological diagnosis. In the case of nasolacrimal duct epithelial infiltration noted during the surgery, removal of pigmented lesions as deep in the nasolacrimal duct as possible would be recommended. In case of local recurrence mainly from the nasolacrimal duct lesion, further radical surgery would not be recommended and molecular target drugs would be better tried in the situation of unresectable tumor after the BRAF mutation is confirmed. Lymph node metastasis and distant metastasis are, of course, the indication of chemotherapy with molecular target drugs. Clinical staging by PET/CT is the standard in the assessment of lacrimal sac melanoma as are melanomas which arise in other sites of the body, including conjunctival melanoma and choroidal melanoma in the field of ophthalmology.

Authors’ Note
Data are available on reasonable request to the corresponding author.

### Table 1. Review of 15 Japanese Patients With Lacrimal Sac Malignant Melanoma Including the Present Patient.

<table>
<thead>
<tr>
<th>Case No./Age/Gender/Laterality</th>
<th>Initial Surgery</th>
<th>Additional Treatment</th>
<th>Local Recurrence</th>
<th>Metastasis</th>
<th>Outcome (Follow-up After Surgery)</th>
<th>Author (Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/50/male/right</td>
<td>Dacryocystectomy</td>
<td>LN dissection</td>
<td>No</td>
<td>Submandibular LN; Preauricular LN</td>
<td>Alive (not described)</td>
<td>Katayama and Terada (1956)</td>
</tr>
<tr>
<td>2/41/female/left</td>
<td>Dacryocystectomy</td>
<td>BCG immunotherapy</td>
<td>No</td>
<td>No</td>
<td>Alive (14 months)</td>
<td>Yamada and Kiragawa (1978)</td>
</tr>
<tr>
<td>3/80/female/right</td>
<td>Dacryocystectomy</td>
<td>Additional extirpation; Dacarbazine/nimustine; LN dissection</td>
<td>No</td>
<td>No</td>
<td>Alive (not described)</td>
<td>Kuwana et al (1979)</td>
</tr>
<tr>
<td>4/59/female/left</td>
<td>Dacryocystectomy</td>
<td>Chemotherapy; vertebrae radiation</td>
<td>No</td>
<td>No</td>
<td>Alive (5 months)</td>
<td>Uchida et al (1990)</td>
</tr>
<tr>
<td>7/78/female/left</td>
<td>Dacryocystectomy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Alive (5 mo)</td>
<td>Matsuo et al (1993)</td>
</tr>
<tr>
<td>8/49/male/right</td>
<td>Dacryocystectomy: Nasolacrimal duct extirpation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Alive (8 months)</td>
<td>Kuwabara and Takeda (1997)</td>
</tr>
<tr>
<td>9/49/male/not described</td>
<td>Dacryocystectomy</td>
<td>Dacarbazine/nimustine/nimustine/ vincristine</td>
<td>Yes</td>
<td>Yes</td>
<td>Dead (2 years)</td>
<td>Goto et al (1999)</td>
</tr>
<tr>
<td>10/71/female/right</td>
<td>Dacryocystectomy</td>
<td>Additional extirpation</td>
<td>Yes</td>
<td>Liver, rib; Pareaocular LN brain, liver, spleen, mediastinum</td>
<td>Dead (1 year)</td>
<td>Ito et al (2004)</td>
</tr>
<tr>
<td>11/60/male/right</td>
<td>Dacryocystectomy</td>
<td>Local radiation: whole brain radiation; dacarbazine/nimustine/carboplatin</td>
<td>No</td>
<td>No</td>
<td>Dead (10 months)</td>
<td>Shinozaki et al (2005)</td>
</tr>
<tr>
<td>13/80/female/left</td>
<td>Dacryocystectomy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Dead (not described)</td>
<td>Nakamura et al (2007)</td>
</tr>
<tr>
<td>14/61/male/right</td>
<td>Dacryocystectomy</td>
<td>Dacarbazine/nimustine/nimustine/ interferon-β</td>
<td>No</td>
<td>No</td>
<td>Alive (10 months)</td>
<td>Maegawa et al (2014)</td>
</tr>
<tr>
<td>15/78/male/left</td>
<td>Dacryocystectomy</td>
<td>Dabrafenib/trametinib</td>
<td>Yes</td>
<td>No</td>
<td>Alive (1.5 years)</td>
<td>Matsuo (this case)</td>
</tr>
</tbody>
</table>

Abbreviations: LN, lymph node; BCG, Bacillus Calmette-Guérin. 
*Not specified.
Author Contributions
TM as an ophthalmologist followed the patient and did the surgery. TT as a pathologist made pathological diagnosis. OY as a dermatologist prescribed molecular target drugs and followed the patient. TM wrote the manuscript; TT and OY did critical review of the manuscript. All authors read and approved the manuscript.

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Ethics Approval
Not applicable to case reports, based on ethical guidelines for medical and health research involving human subjects issued by the Government of Japan.

Informed Consent
Oral informed consent was obtained from the patient.

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