

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

Journal of Investigative Medicine High Impact Case Reports
Volume 7: 1–6
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DOI: 10.1177/2324709619888052
journals.sagepub.com/home/hic


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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 ($SUV_{max} = 10.29$ 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.¹ 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.²⁻²⁴

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.²⁵⁻³⁷

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

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Received September 20, 2019. Accepted October 16, 2019.

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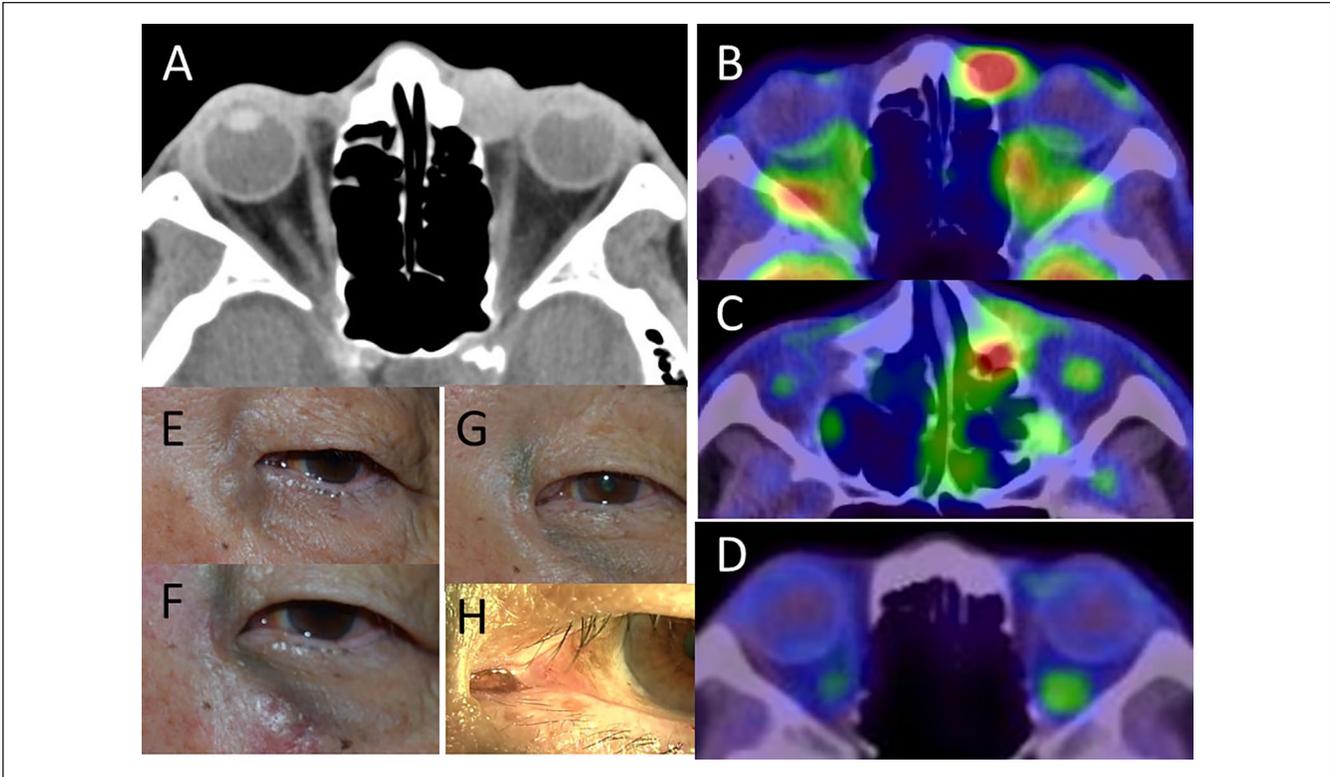


Figure 1. Lacrimal sac mass (E) on the left side on computed tomographic scan (A) at the initial presentation in a 78-year-old man. About 1 month after dacryocystectomy, subcutaneous pigmented lesions (F) were noted and whole-body 2- 18 F-fluoro-2-deoxy-D-glucose positron emission tomography fused with computed tomography (PET/CT) showed 2 high-uptake sites at the levels of medial canthus ($SUV_{max} = 10.29$, B) and nasolacrimal duct ($SUV_{max} = 15.38$, 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).

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- 18 F-fluoro-2-deoxy-D-glucose positron emission tomography fused with computed tomography (PET/CT) showed 2 high-uptake sites ($SUV_{max} = 10.29$ and 15.38) at the levels of the medial canthus (Figure 1B) and nasolacrimal duct (Figure 1C), with no abnormal uptake found in the other sites of the body. The lesion had the BRAF V600E mutation by a US Food and Drug Administration–approved test (the cobas 4800 BRAF V600 Mutation Test; Roche Molecular Diagnostics, Pleasanton, CA), and he showed no rise of serum 5-S-cysteinyldopa at 5.7 nmol/L (normal range = 1.5–8.0). Two months after the surgery, he began to take oral dabrafenib (Tafinlar) 300 mg daily plus trametinib (Mekinist) 2 mg daily. In half a year, the subcutaneous and nasolacrimal ductal recurrent lesions resolved (Figure 1G), and PET/CT showed no abnormal uptake in the orbit on the left side (Figure 1D), with no abnormal uptake at other sites of the body. Conjunctival pigmentation in the lacrimal caruncle on the left side (Figure 1H) remained unchanged in comparison with the initial visit. At the last visit, 1½ years after the initial visit, PET/CT showed small weak uptake sites in cervical and axillary lymph nodes. He had the stable disease in good physical status with the continuing

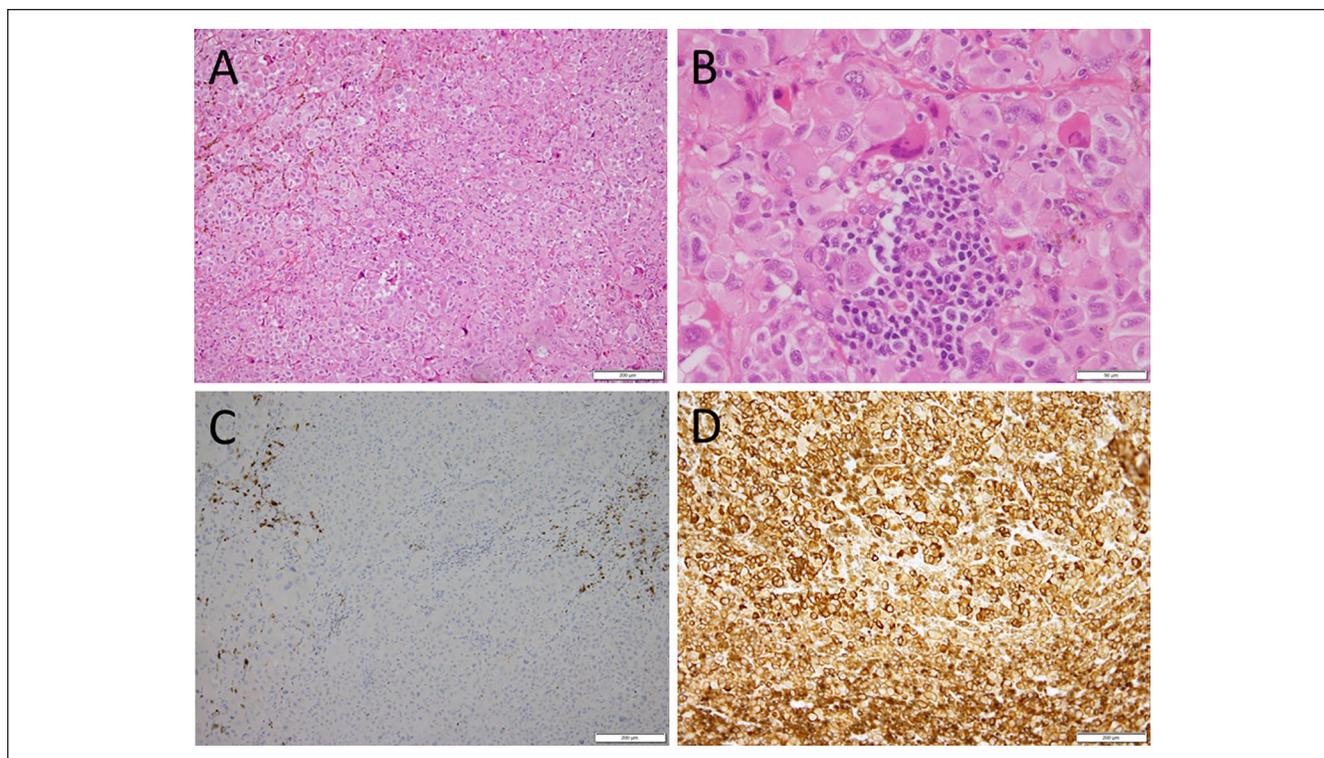


Figure 2. Pathology of lacrimal sac melanoma. (A) Large epithelioid cells with abnormal nuclei arranged in irregular strands and foci. (B) Small lymphocytes infiltrated as a focus among large neoplastic cells. The neoplastic cells are negative for keratin AE1/AE3 (C), and positive for cocktail-mix antibodies against tyrosinase, melan A (MART-1, melanoma antigen recognized by T cells-1), and HMB45 (D). Scale bar = 200 μ m in A, C, and D. Scale bar = 50 μ m in B.

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 melanoma (in Japanese)” in *Igaku Chuo Zasshi* (Japan 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.^{38,39} The patient maintained the stable disease with no local recurrence but with small

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

Case No./Age/ Gender/Laterality	Initial Surgery	Additional Treatment	Local Recurrence	Metastasis	Outcome (Follow-up After Surgery)	Author (Year)
1/50/male/right	Dacryocystectomy	LN dissection	No	Submandibular LN; Preauricular LN	Alive (not described)	Katayama and Terada ²⁵ (1956)
2/41/female/left	Dacryocystectomy	BCG immunotherapy	No	No	Alive (14 months)	Yamada and Kitagawa ²⁶ (1978)
3/80/female/right	Dacryocystectomy	Additional extirpation	Yes	No	Alive (not described)	Kuwana et al ²⁷ (1979)
4/59/female/left	Dacryocystectomy	Dacarbazine/nimustine; LN dissection	No	Cervical LN	Alive (5 months)	Uchida et al ²⁸ (1990)
5/52/female/right	Orbital exenteration	Dacarbazine/nimustine/ vincristine	No	No	Alive (not described)	Takahashi et al ²⁹ (1991)
6/57/female/left	Dacryocystectomy	Dacarbazine; LN dissection	No	Submandibular LN	Alive (8 months)	Matsune et al ³⁰ (1992)
7/78/female/left	Dacryocystectomy	No	No	No	Alive (5 mo)	Matsuo et al ³¹ (1993)
8/49/male/right	Dacryocystectomy; Nasolacrimal duct extirpation	Chemotherapy ^a ; vertebrae radiation	No	Thoracic vertebrae	Not described	Kuwabara and Takeda ³² (1997)
9/49/male/not described	Dacryocystectomy	Dacarbazine/nimustine/ vincristine	Yes	Yes	Dead (2 years)	Goto et al ³³ (1999)
10/71/female/right	Dacryocystectomy	Additional extirpation	Yes	Liver, rib	Dead (1 year)	Ito et al ³⁴ (2004)
11/60/male/right	Dacryocystectomy	Local radiation; whole brain radiation; dacarbazine/ nimustine/carboplatin	No	Preauricular LN brain, liver, spleen, mediastinum	Dead (10 months)	Shinozaki et al ³⁵ (2005)
12/69/male/left	Dacryocystectomy	Local interferon- β injection	No	No	Alive (8 months)	Nakamura et al ³⁶ (2007)
13/80/female/left	Dacryocystectomy	No	No	Liver, lung	Dead (not described)	Nakamura et al ³⁶ (2007)
14/61/male/left	Dacryocystectomy	Dacarbazine/nimustine/ vincristine; interferon- β	No	Liver, stomach, lung, brain	Dead (10 months)	Maegawa et al ³⁷ (2014)
15/78/male/left	Dacryocystectomy	Dabrafenib/trametinib	Yes	No	Alive (1.5 years)	Matsuo (this case)

Abbreviations: LN, lymph node; BCG, Bacillus Calmette-Guérin.

^aNot specified.

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,^{38,39} 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 melanoma³⁹ and choroidal melanoma⁴⁰ in the field of ophthalmology.

Authors' Note

Data are available on reasonable request to the corresponding author.

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.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article:

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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