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From apparent pseudoprogression to durable complete remission of expansile destructive sinonasal mucosal melanoma under pembrolizumab after primary endoscopic resection: A case report

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Abstract

Head and neck mucosal melanoma is a rare but highly aggressive malignant tumor that usually has a poor prognosis. We describe a 53-year-old male patient, having no any medical history, with left maxillary sinus mucosal melanoma causing bilateral lung metastasis. Rapid tumor regrowth was observed on the 49th day after radical tumor resection. Subsequent pembrolizumab immunotherapy initially elicited pseudoprogression, for which add-on radiation therapy was carried out during maintenance pembrolizumab. A gradual decrease in tumor volume and complete remission were observed by a series of magnetic resonance imaging scans and lung windows of a computer tomography scan of chest. At the 29-month follow-up, the patient was rendered disease-free. In conclusion, head and neck mucosal melanoma may regrow rapidly after surgical resection and pseudoprogression could be frightening during immunotherapy. Subsequent single-agent pembrolizumab plus localized radiation therapy aiming to release more tumor antigens may offer the possibility of long-term remission.

Keywords

Sinonasal melanoma, pembrolizumab, pseudoprogression

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Introduction

Head and neck mucosal melanoma (HNMM) is relatively rare compared with cutaneous melanoma. It accounts for 1%–4% of all melanoma diagnoses and 0.03% of all cancer diagnoses.[1,2] The nasal cavity, paranasal sinuses, oral cavity, pharynx, larynx, and upper esophagus may be involved, in decreasing order of frequency.[3,4] In addition to its rarity, HNMM is an aggressive malignant tumor with a poor prognosis.[5,6] This case report was approved by our hospital's Institutional Review Board (IRB-11122).

Case presentation

A 53-year-old male visited our Otolaryngology Department due to yellowish nasal discharge for over a month. After a physical examination, computed tomography (CT) was performed, which revealed a left maxillary sinus tumor. Therefore, we performed endoscopic left maxillary sinus tumor biopsy, and the pathology revealed that it was malignant melanoma (Figure 1(a)). Next, magnetic resonance imaging (MRI) was performed, which further identified tumor invasion of the adjacent soft tissue and bone (Figure 2(a)). Figure 2 presents the gradual alterations in both imaging and facial appearance before and after treatment. Subsequent cancer workup with chest CT scans demonstrated bilateral lung metastases (Figure 3(a) and (b)). Figure 3 compares the imaging of lung metastasis before and after immunotherapy. After transarterial

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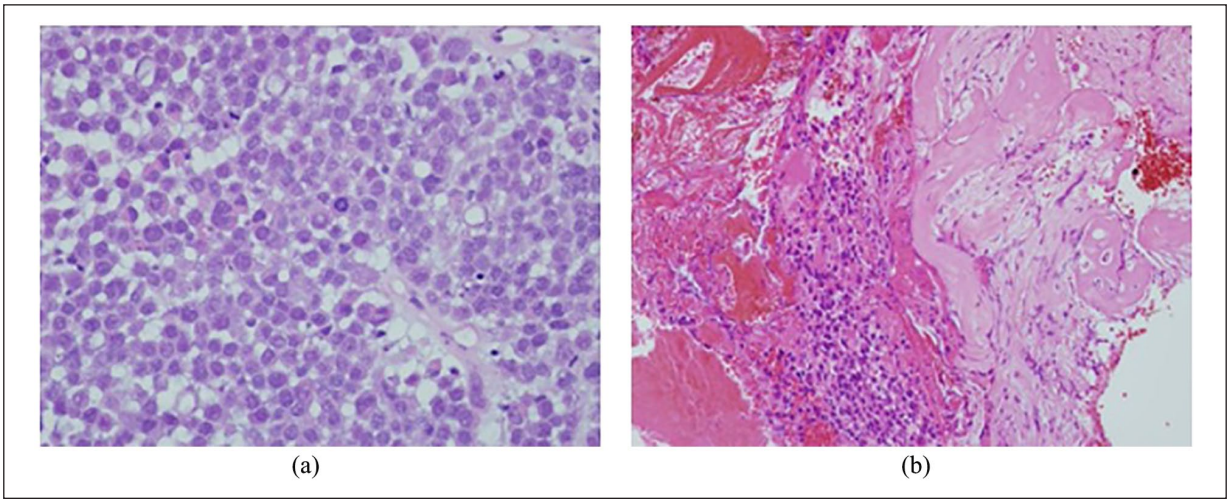

Figure 1. (a) Mucosal melanoma in left maxillary sinus. Tumor cells show epithelioid morphology, with high nuclear–cytoplasmic ratio, round and hyperchromatic nuclei, and brisk mitoses. (b) Prasad's microstage: level III. Tumor cell infiltration in trabecular bone.

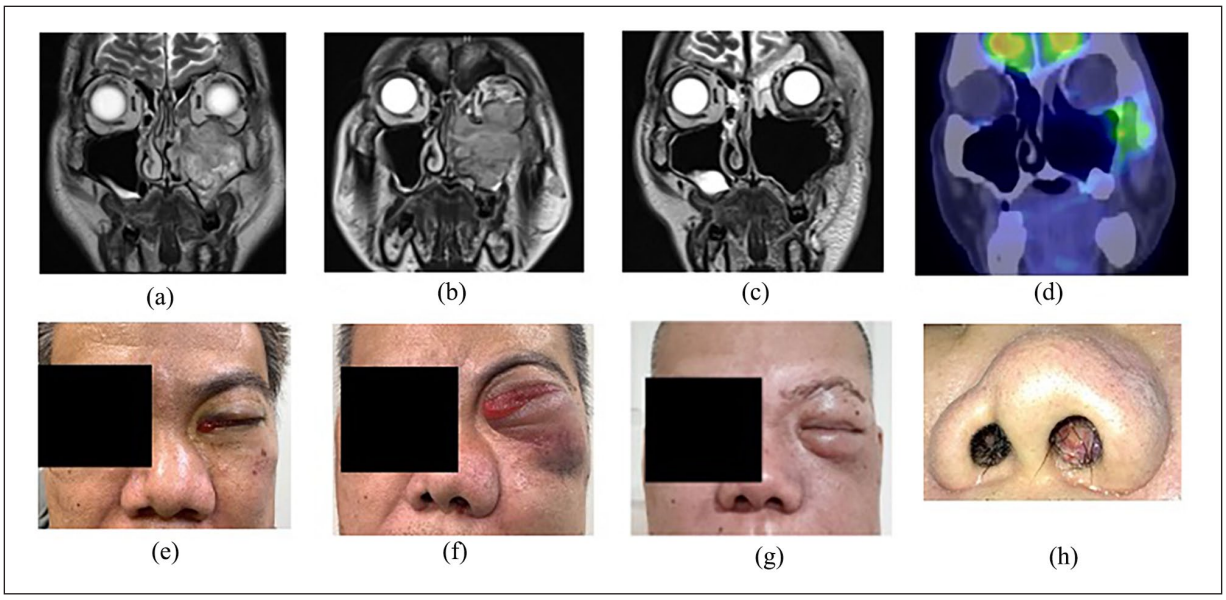

Figure 2. (a) Magnetic resonance imaging (MRI) before tumor resection. (b) MRI showing rapid tumor regrowth. (c) MRI showing complete tumor remission. (d) Positron emission tomography (PET) scan confirmed tumor remission. (e)–(g) demonstrate the progression and improvement of left orbital protrusion. (h) The tumor can be seen through the left nostril.

embolization of the ipsilateral internal maxillary artery, endoscopic radical tumor excision via the prelacrimal recess approach was performed.[7] The disease extent was evaluated via endoscopy. Pathology assessment revealed that the tumor cells infiltrated in trabecular bone. Prasad's microstage is level III (Figure 1(b)).[8] According to the 7th edition of the American Joint Committee on Cancer staging for HNMM, the staging of this case of malignant melanoma was T4aN0M1, stage IVB.[9] After radical tumor excision, two cycles of single-agent dacarbazine at 800 mg/m^2 at an interval of 3 weeks were administered, which was required as an immunotherapy bridging therapy by the local National Health Insurance policy. Additionally, an endonasal sinuscopy was performed for follow-up on the 7th day and 28th day after radical tumor excision. No evidence of tumor recurrence was observed.

Unfortunately, left orbital swelling and blurred vision were noted gradually (Figure 2(e)). An MRI on the 49th day after radical tumor resection revealed rapid regrowth of the left maxillary melanoma. The tumor was approximately 7 cm in size and involved the maxillary sinus, maxilla bone, nasal cavity, orbital floor, cheek region, and masticator space (Figure 2(b)). Marked proptosis was also noted due to the compression of the tumor.

Pembrolizumab immunotherapy was started on the 58th day after radical tumor resection, and intensity-modulated radiation therapy (IMRT) was arranged on the 92nd day

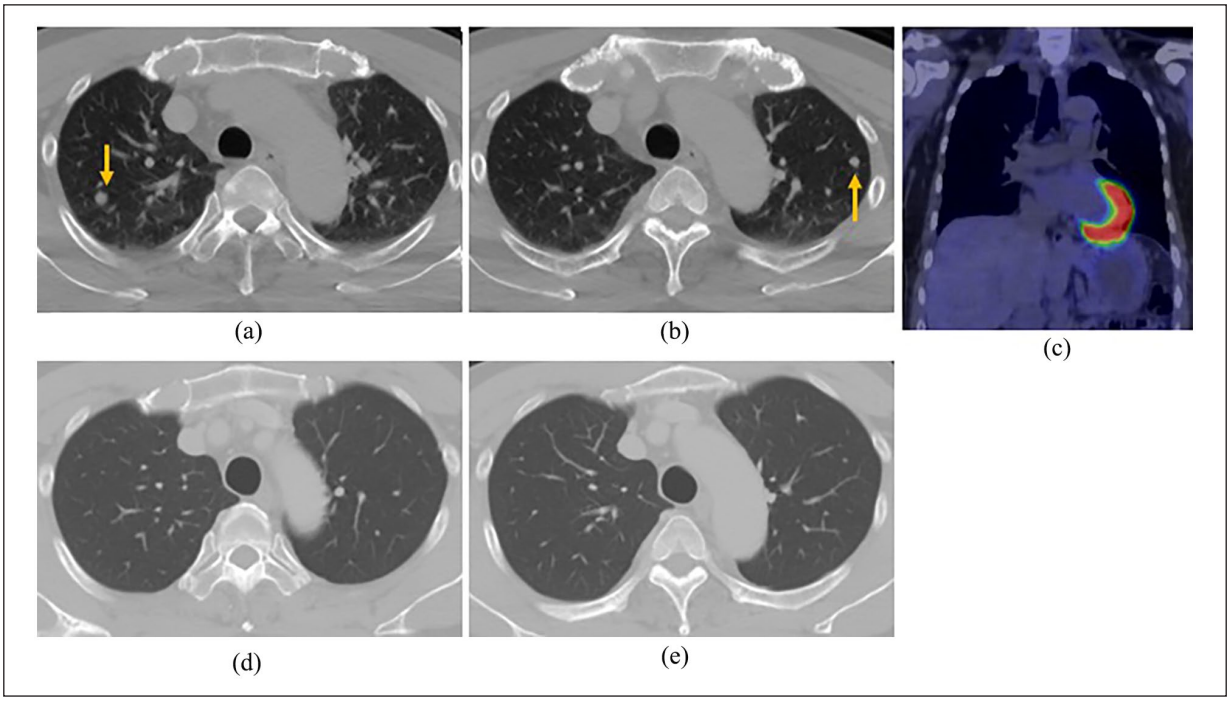

Figure 3. (a) and (b) Bilateral lung metastases. (c) PET scan confirmed tumor remission. (d) and (e) Bilateral lung metastases were ablated.

because of the follow-up imaging demonstrated more bulky disease. A combination of antiprogrammed cell death 1 inhibitor and anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor was discussed. However, the patient could not afford nonreimbursed anti-CTLA4 inhibitor. The first dose of IMRT was arranged after 34 days of pembrolizumab immunotherapy. Before IMRT, apparent progressive left orbital protrusion was observed in 4 weeks (Figure 2(f)), which was now considered pseudoprogression after two cycles of pembrolizumab immunotherapy. At this time, the colossal regrowth tumor could be directly seen through the left nostril (Figure 2(h)). The course of IMRT lasted 7 weeks. However, the patient decided not to complete the course due to the COVID-19 pandemic.

After combining immunotherapy and radiation therapy, proptosis gradually decreased. MRI on the 167th day after radical tumor resection showed a decreased tumor size (4.1 cm). After regular immunotherapy treatment, MRI on the 294th day after radical tumor resection revealed a widening left osteomeatal complex without an apparent mass lesion (Figure 2(c)). Also, the swollen left orbital has improved in appearance (Figure 2(g)). Complete remission was achieved. Additionally, chest CT showed that the bilateral upper lung metastases were ablated by immunotherapy (Figure 3(d) and (e)). Figure 4 depicts an imaging series showing tumor pseudoprogression to complete remission. Currently, the patient is under regular follow-up at the medical oncology outpatient department. In the latest follow-up examination, a positron emission tomography scan demonstrated no tumor recurrence or metastasis (Figure 2(d) and 3(c)).

Discussion

HNMM treatment typically involves radical tumor resection, which is considered the cornerstone of the management of this cancer.[10,11] However, HNMM is often resistant to chemotherapy and radiotherapy. Radiotherapy may be an adjuvant or exclusive treatment to benefit local control and overall survival.[10] Other treatments, such as targeted therapies and immunotherapies, may also be used in some cases.[12] Targeted therapies include BRAF inhibitors, MEK inhibitors, and c-KIT inhibitors. Immune checkpoint inhibitors are immunotherapy drugs that block different checkpoint proteins, such as anti-CTLA-4, anti-programmed cell death 1, and anti-programmed death-ligand 1 inhibitors, from binding to their partner proteins. This prevents the "off" signal triggered by the binding between checkpoint and partner proteins from being sent, allowing T cells to kill cancer cells.[13]

The current literature has only a few studies dedicated to applying immune checkpoint inhibitors for HNMM. Pembrolizumab has been studied as a potential therapeutic agent for HNMM.[14] A post hoc analysis of the KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006 trials found that pembrolizumab had durable antitumor activity in advanced mucosal melanoma regardless of prior ipilimumab treatment.[15] A pooled analysis with patients who had a confirmed histologic diagnosis of unresectable stage III or stage IV (advanced) mucosal melanoma was analyzed by D'Angelo et al. The results show that, for mucosal melanoma treated with nivolumab alone, the median progression-free survival was 3.0 months (95% confidence interval: 2.2–5.4 months)

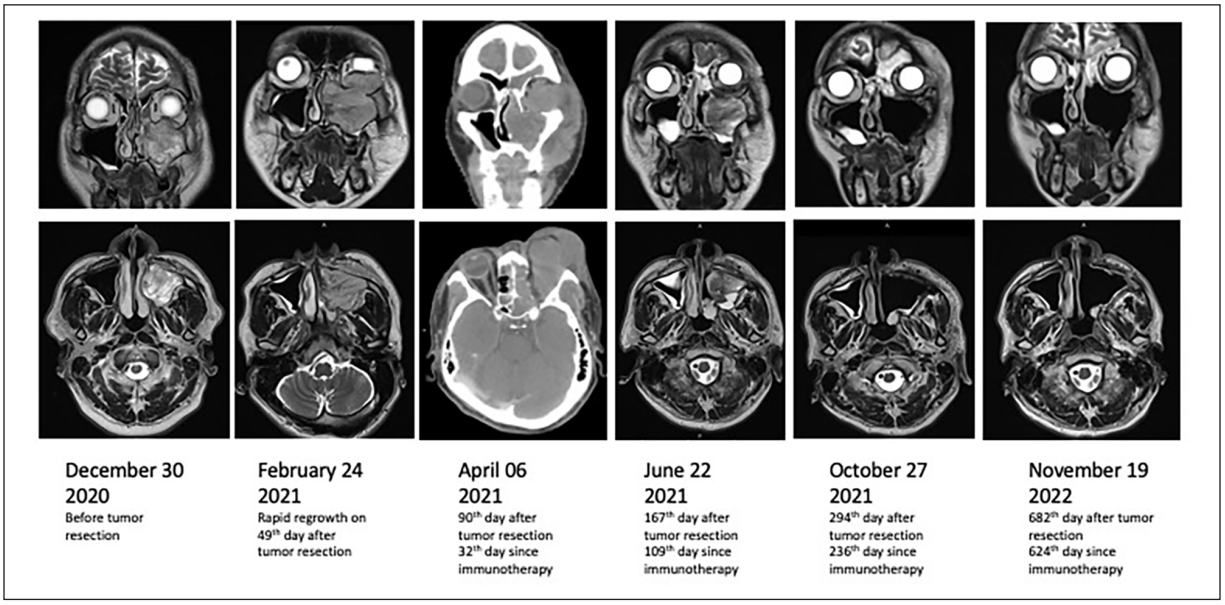

Figure 4. Imaging series of tumor pseudoprogression to complete remission.

and the objective response rate was 23.3% (95% confidence interval: 14.8%–33.6%). For mucosal melanoma treated with nivolumab in combination with ipilimumab, the median progression-free survival was 5.9 months (95% confidence interval: 2.8 months to not reached), and the objective response rate was 37.1% (95% confidence interval: 21.5%–55.1%).[16]

We leveraged the salvage radiation therapy for this patient with two main purposes. First, to assist control of the expansile tumor, and second, to release more tumor antigens that could potentiate the immunotherapy effect.[17]

Pembrolizumab combined with IMRT indeed demonstrated efficacy in combating HNMM in our patient. MRI revealed complete tumor remission 236 days after immunotherapy and no tumor recurrence or tumor metastasis for more than 29 months. In conclusion, HNMM may show rapid regrowth after surgical resection, in which case immunotherapy with radiotherapy may offer the possibility of long-term remission.

Conclusions

HNMM may regrow rapidly after surgical resection. Subsequent single-agent pembrolizumab plus localize radiation therapy may offer the possibility of long-term remission.

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Author contribution

H.C.L. and P.H.S. conceived the research question. V.C.K. supervised the research project. V.C.K. and H.C.L. were responsible for methodology and data curation. V.C.K. and H.C.L. analyzed and interpreted the study output. H.C.L. wrote the original draft. V.C.K. and P.H.S. reviewed and edited the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The image data used to support the findings of this study are included within the article.

Declaration of conflicting interests

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Ethics approval

Ethical approval to report this case was obtained from Kuang Tien General Hospital Institutional Review Board (IRB-11122).

Informed consent

This case report was approved by the Institutional Review Board of Kuang Tien General Hospital (IRB-11122). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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