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Primary non-cutaneous melanomas of the head and neck: Case series and review of the literature

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Abstract

Primary non-cutaneous melanoma is a rare type of melanoma that occurs mostly on mucosal surfaces. The head and neck region is the most common site for these melanomas. The following cases described herein include patients diagnosed with primary non-cutaneous melanomas. The locations included the parotid gland (one case), the submandibular gland (one case), and the nasal cavity and paranasal sinuses (three cases). Among these patients, one patient developed lymph node metastasis and one patient had distant metastasis. Treatment included endoscopic surgery (one case), endoscopic surgery with adjuvant radiotherapy (one case), open surgery (one case), and palliative chemotherapy (one case). One patient refused to receive treatment. After treatment, one patient had local recurrence. A local and distant recurrence was noted in one case. This report aims to describe clinical features, treatment options, and prognosis of primary non-cutaneous melanomas of the head and neck.

Keywords

Melanoma, mucosa, salivary glands, treatment, prognosis

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Introduction

Primary non-cutaneous melanomas (CM) of the head and neck, including primary mucosal melanoma (PMM) and the less common but equally enigmatic primary salivary gland melanoma (PSGM), represent a challenging group of malignancies in oncology. These melanomas, which originate in the mucous membrane of the head and neck as well as the salivary glands, are characterized by their rarity and distinctive anatomical locations.[1–3]

PMM represents 0.03% of all cancers and 0.8%–3.7% of all melanomas.[1–3] The majority of PMMs (41%–55%) occur in the head and neck region.[4] The most common sites of PMMs of the head and neck are the nasal cavity, the paranasal sinuses, and the oral cavity.[1] PSGMs are extremely rare and only a few cases have been described in the literature.[4]

This report aims to describe clinical features, treatment options, and prognosis of primary non-CM of the head and neck.

Materials and methods

In this case series, all primary non-CM of the head and neck treated at our department from 1995 to 2022 were retrospectively reviewed. Clinical and imaging findings, treatment offered, pathology findings, and outcomes were collected.

Case reports

Case 1

A 54-year-old male patient presented with a growing painless swelling on the right parotid region and a headache lasting for 2 months.

Physical examination revealed a firm, regularly shaped swelling, located in the right parotid region. It was fixed to the underlying structures, measuring 6 cm with normal overlying skin. Facial movements were normal on examination. Intraoral, rhinologic, ophthalmic, and cutaneous exams were

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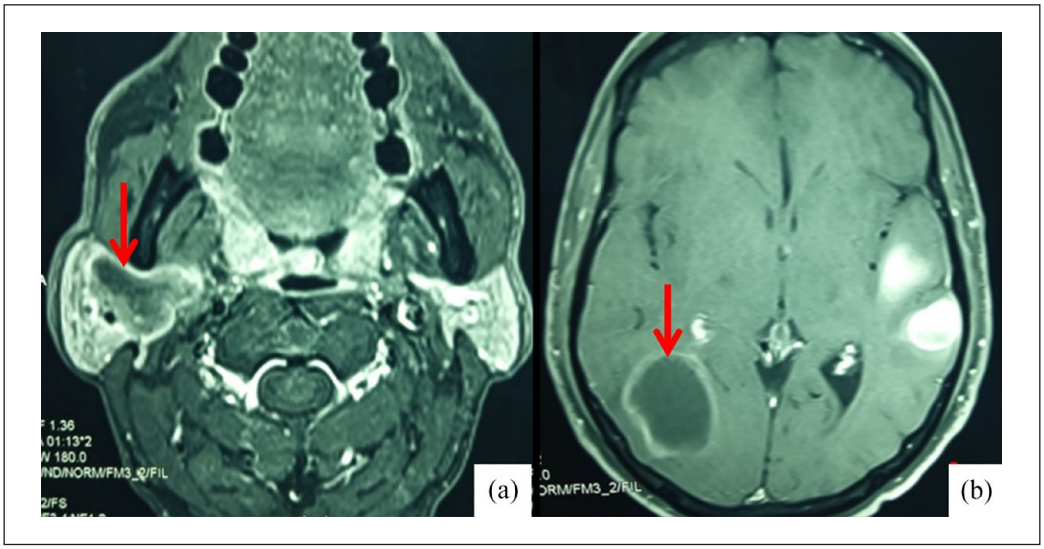

Figure 1. (a) Magnetic resonance imaging T1 sequence post-contrast (axial section): the tumor (arrow) occupying the superficial and the deep lobe of the right parotid gland not showing enhancement. (b) Computed tomography post-contrast (axial section): cerebral metastasis (arrow).

unremarkable. No cervical lymphadenopathy was palpated. Magnetic resonance imaging (MRI) revealed a tumor occupying the superficial and the deep lobe of the right parotid gland (Figure 1(a)). Peroperatively, it infiltrated the surrounding structures (facial nerve, internal jugular vein, external carotid artery). Therefore, the tumor could not be resected. A biopsy was performed. Histologic examination confirmed the diagnosis of an undifferentiated cancer. Immunohistochemical analysis revealed the tumor to be a malignant melanoma as it expressed HMB-45 and Melan-A. Complete screening revealed cerebral and pulmonary metastases. The diagnosis of primary melanoma of the parotid gland with cerebral (Figure 1(b)) and pulmonary metastases was made. Palliative chemotherapy was indicated but the patient died 1 month later before receiving further treatment.

Case 2

An 87-year-old woman presented with a 2-year history of left-sided neck swelling, gradually increasing in size.

On examination, a 7-cm swelling was palpated in the left submandibular region. It was hard, painful, and fixed to the underneath tissues. There were no other neck swellings. The oral cavity, nasal cavity, and oropharynx were unremarkable on examination. Cutaneous and ophthalmic exams were normal.

An ultrasound-guided fine needle aspiration suggested a melanoma. On computed tomography (CT), the tumor occupied the left submandibular region; it eroded the mandibular bone and extended to the parotid region. There was no evidence of lymph node or distant metastasis.

Following this, a biopsy was performed. On Histologic examination, the diagnosis of a submandibular melanoma was confirmed.

The patient refused to receive radiotherapy. She died 18 months following the surgery.

Case 3

A 70-old-year woman, presented with left nasal obstruction and recurrent epistaxis. The nasal exam showed a pigmented mass occupying the whole left nasal fossa. No cervical lymphadenopathy was palpated. Ophthalmic and cutaneous exams were unremarkable. On CT, the tumor extended into the left ethmoid and maxillary sinuses. A biopsy of the mass revealed the diagnosis of melanoma. An open surgery was done. The tumor invaded the maxillary bone. It was resected along with the invaded bone. The maxillary defect was managed by a prosthesis. There was no evidence of nodal or distant metastasis on imaging. After a follow-up of 6 years, the nasal endoscopy showed no sign of tumor recurrence and the patient remained symptom-free.

Case 4

A 90-year-old woman complained of left nasal obstruction and recurrent epistaxis, lasting for 6 months. Nasal endoscopy revealed a tumor of the left nasal cavity that extended posteriorly to the rhinopharynx. Several cervical lymph nodes were palpated. The most voluminous one measured 3 cm. Ophthalmic and cutaneous exams were unremarkable. On CT and MRI, the tumor extended to the left maxillary sinus, and bilateral suspicious lymph nodes were found. The biopsy of the nasal tumor revealed a melanoma. Complete screening did not reveal distant metastases. A transnasal endoscopic tumor resection was performed followed by radiotherapy of the primary tumor and the cervical nodes. Neck

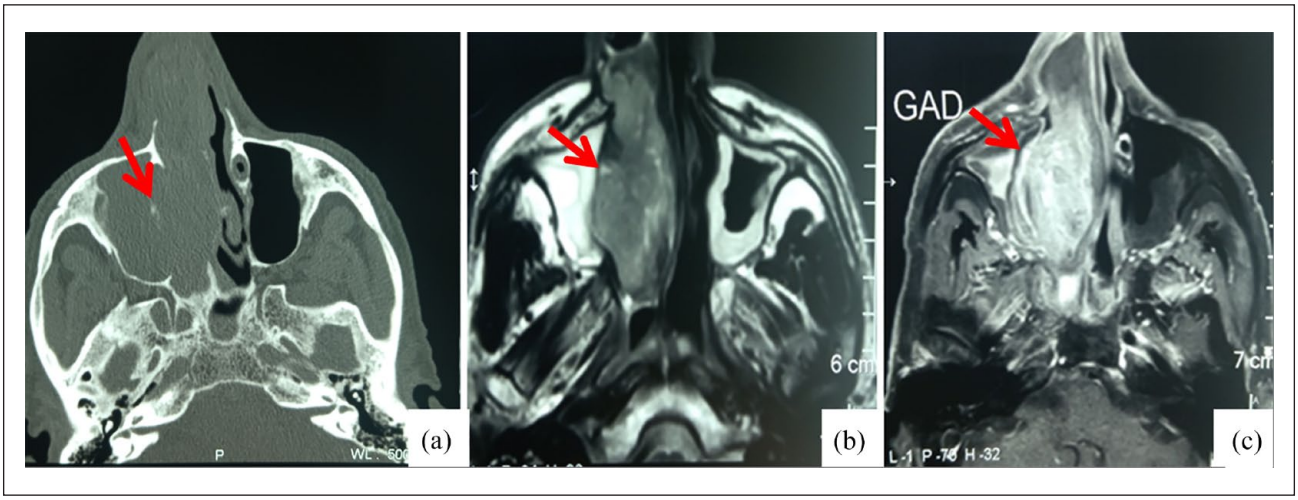

Figure 2. (a) Computed tomography scan (axial section): tumor (arrow) involving the right nasal cavity with bony erosion of the nasal septum and the medial maxillary sinus wall. (b) Magnetic resonance imaging (MRI) T2 sequence (axial section): tumor showing hypointense signal. (c) MRI T1 post-contrast (axial section): tumor showing enhancement.

dissection was not performed as the patient presented a high risk of anesthesia. Two years after surgery, the patient presented with local recurrence and bone metastasis.

Case 5

A 70-old-year man, presented with a 5-month history of right nasal obstruction and recurrent epistaxis. The nasal exam showed a mass filling the right nasal cavity. Ophthalmic and cutaneous exams were unremarkable. No cervical lymphadenopathy was palpated.

CT and MRI showed a tumor involving the right nasal cavity with bony erosion of the nasal septum and the medial maxillary sinus wall (Figure 2).

A biopsy of the tumor was performed. It showed an undifferentiated tumor with immunohistological features of a melanoma. The tumor stained positively for S-100, HMB-45, and Melan-A. Complete screening did not reveal metastatic lymph nodes or distant metastases. A complete resection of the tumor was performed endoscopically. Four months after surgery, the patient presented with epistaxis. It was due to a local recurrence. An endoscopic surgical resection was conducted two additional times followed by radiation therapy. The patient was free of disease 2 years after surgery.

Discussion

Compared to CM, the biology and pathogenesis of primary non-CM of the head and neck are poorly understood.[1,2] Melanocytes are melanin-producing cells located mainly in the skin, although they can be found in other tissues such as the eyes and mucosae of the head and neck.[1,2] The role of melanocytes in the mucosae is not well understood, even though some studies have suggested that melanocytes participate in the immune response.[1,2] Unlike mucosae, melanocytes are not embryologically present in salivary glands however some reviews reported their existence in salivary glands.[5] To explain this finding, some theories have supported that they can arise from the mucosa of the oral cavity.[5]

The nasal cavity and paranasal sinuses are the commonest sites of PMMs,[1,2] as described in our series. Melanomas of the submandibular and the parotid gland are usually metastatic of a CM as these glands are known to be filtering centers for lymphatic drainage of the head and neck area.[4] However, a few cases of PMSGs have been described in the literature.[4,5]

Most series report a similar distribution between males and females[1] and between races.[3] PMMs occur in a median age of 60 years, although they can happen in any age group.[1,2] The mean age of our patients was 74 years.

Many risk factors have been associated with PMM such as mucosal nevi and cigarette smoking in oral mucosal melanoma (OMM), formaldehyde in sinonasal mucosal melanoma (SNMM), and family history of PMM.[1,2] However, unlike CM, PMMs are not associated with racial pigmentation, sun exposure, and some viruses (human papillomavirus, human herpes virus, or polyomavirus).[1–3]

When diagnosing a primary non-CM, especially in some sites in which it rarely arises, the possibility of metastatic lesions from CM or ocular melanoma should be excluded.[6] Skin and ophthalmic examination must be performed.[3,6] The melanoma can also be metastatic of a regressed primary elsewhere.[5] In fact, regression may be seen in about 10%–35% of melanomas.[5] Compared to PMM, PGSM's diagnosis is more difficult and a true dilemma as salivary glands contain lymph nodes responsible for the drainage of the head and

neck skin and mucosa, which makes it a common site of metastatic nodes.[5] Therefore, the predominant tumor mass should be intraglandular; with no evidence of lymph node tissue present in the mass and no evidence of melanoma in other locations.[4]

For the two cases involving melanomas of the parotid gland and the submandibular gland, the possibility of either a PSGM or a metastatic intraglandular node was considered. The PSGM was the most likely diagnosis because there was no evidence of a primary tumor on the physical exam or on the CT scan. Furthermore, the tumor did not contain any lymph node tissue. Also, the patients did not report any cutaneous lesions that regressed.

Usually, clinical presentation in melanomas is similar to other primary cancers arising in the same site.[1]

In PMM of the head and neck, lymph node involvement is unusual at the time of presentation.[1] Furthermore, the presence of nodal involvement without distant metastasis is quite rare.[1]

Compared to OMMs, nodal metastases in SNMMs are less frequent (25% vs 6%, respectively) at initial presentation and (42% vs 20%, respectively) during the course of the disease.[1]

In primary melanoma of the parotid and the submandibular gland, regional and distant metastases are common.[4]

Histological features are used in the diagnosis of melanoma including architectural and cytological features.[7] However, in some cases, immunohistochemistry can be necessary for diagnosis.[2]

PMMs are likely to stain positively for S-100, Vimentin, HMB-45, Melan-A, and SOX10; and negatively for Cytokeratin and Epithelial Membrane Antigen.[2] S100 is a sensitive marker for melanoma, while SOX10 is highly specific for this tumor.[8]

These markers are also expressed by PSGMs.[9] However, it has been reported a few cases of other salivary gland tumors, including carcinomas, staining positively for melanocytic markers.[10]

Recently, PRAME (PReferentially expressed Antigen in MElanoma) has been introduced as a useful diagnostic tool in the differential diagnosis between benign and malignant melanocytic lesions.[11] According to Ricci et al.,[11] high PRAME expression ($\geqslant$60%) in mucosal melanocytic tumors was highly suggestive of melanoma.

In two of the reported cases, the diagnosis of melanoma could not be performed based on histomorphologic features. Immunohistology was necessary for the diagnosis.

CT and MRI are useful to determine the extent of the tumor.[1] Melanomas have a high signal intensity on T1-weighted images (especially in highly melanotic tumors), low signal intensity on T2-weighted images, and enhancement on T1-weighted images.[1]

Also, because of the high fluorodeoxyglucose (FDG) avidity of melanomas, FDG-positron emission tomography is useful in the staging of these tumors.[1]

For PMMs, many staging systems have been proposed.[1]

The Ballantyne staging system classifies PMMs into three stages: stage I for localized tumors, stage II for cervical lymph node metastasis, and stage III for distant metastases.[1] This system is simple and can be reproduced for all PMMs, regardless of their location.[1] However, it does not consider the local extension and emphasizes too much on the regional spread, which is uncommon in PMMs.[1]

Prasad et al. subdivided the Ballantyne Stage I category into three sub-categories according to the depth of infiltration within the mucosa: level 1 (in situ disease), level 2 (superficially invasive: melanoma invading up to the lamina propria), and level 3 melanomas (deeply invasive: muscle, bone, or cartilage).[1] This staging system is histological: it can only be determined after surgery.[1]

PMM of the head and neck can also be staged according to the AJCC TNM classification for epithelial cancers or according to the specific TNM classification for PMM (mmTNM) that includes the depth of infiltration of the tumor.[1]

Some studies have demonstrated the superiority of the TNM classification for epithelial cancer over the Ballantyne, Prasad, and/or the specific TNM classifications for PMMs.[1,2]

In treating PMMs, complete resection with clear margins is one of the most important prognostic factors.[2] However, this goal is not easily achieved due to the anatomical complexity of the head and neck region.[2] For locally advanced tumors, wide and radical surgery should be performed to obtain negative surgical margins.[2] Otherwise, less morbid treatments such as endoscopic surgery can be performed and seem to have a similar oncological efficacy.[12]

The United Kingdom guidelines released in 2020 recommend endoscopic surgery for sinonasal PMMs when clear margins can be granted.[13]

For patients without lymph node metastases on clinical exam and on imaging at diagnosis, treatment options include clinical and radiological follow-ups; surgical intervention (sentinel lymph node biopsy or elective neck dissection); adjuvant irradiation; or adjuvant systemic therapy.[13]

In SNMM, lymph node metastases are not frequent.[3] Therefore, neck dissection should be reserved for patients with clinically evident nodal involvement,[3] unlike OMM where nodal involvement is more common, and where prophylactic neck dissection is an independent prognostic factor.[14]

For recurrent disease without distant metastasis, a salvage surgery should be performed every time a complete removal of the tumor can be obtained.[1,2] It could save up to 25% of these patients.[1,2]

Although PMM has been considered a radioresistant tumor, an intertumor heterogeneity in response to radiotherapy has been demonstrated through clinical studies.[1]

Radiotherapy alone can be used with curative intent and is associated with similar survival rates compared to surgery alone.[15] It is recommended for inoperable patients, patients

who refuse surgery, and patients suffering from unresectable tumors.[13] The national comprehensive cancer network guidelines for mucosal melanoma recommend radiotherapy alone for unresectable locally advanced cases.[16]

Adjuvant radiotherapy is recommended in advanced and recurrent cases, in case of positive or close margins and for multiple primary lesions.[13] It can be considered for patients with nodal metastases.[1]

A recent meta-analysis, published in 2020 including 2489 patients treated for PMM, showed that surgery with adjuvant radiotherapy confers a lower risk of local recurrence and a better overall survival when compared to surgery alone, without a significant difference in rates of distant metastases.[13] However, according to the revue by Ascierto et al.,[2] radiotherapy seems to improve local control, but its impact on overall survival may be limited.

Palliative radiotherapy is recommended for symptomatic metastatic disease.[2]

Distant metastasis in PMM of the head and neck is frequent justifying the need for systemic therapy for metastatic tumors.[17]

Treatment approaches for PMM have been influenced by advancements made in the treatment of CM. The integration of new therapies (such as targeted therapy and immunotherapy) for PMM of the head and neck primarily relies on insights gained from trials focused on CM.[16,18] Intriguingly, in the latter trials, mucosal sites are frequently excluded. This exclusion significantly influences our understanding of therapies for these types of tumors.[2,3]

To identify potential therapeutic targets, some genetic alterations have been identified such as: c-KIT overexpression (80% of PMMs) and somatic mutations (10%–30% of PMMs), MITF amplification (15%–20% of PMMs), BRAF mutations (<10% of PMMs), RAS mutations (20% of PMMs), overexpression (90% of PMMs), and CDKN2A mutations (50% of PMMs).[1,2]

Several molecules have been tested such as chemotherapy (temozolomide, cisplatin, dimethyl triazine imidazole carboxamide. . .), immunotherapy (anti-PD1, anti-CTLA-4, interferon α), and targeted therapies (BRAF/MEK, C-KIT). . .[19]

The evidence base is generally of low quality, with selection bias (the treatments are generally used for treating disseminated disease and for palliation) and a high level of imprecision.[13] They include a few numbers of patients, PMMs from other anatomical sites or CM.[13]

PMMs seem to have a better response to chemotherapy (temozolomide or/and cisplatin) than to interferon α.[19]

Recent studies have demonstrated that PMM has a better response to immune therapy (anti-PD1, anti-CTLA-4) than chemotherapy.[13]

Anti-PD1 combined with anti-CTLA-4 seems to have greater efficacy than either agent alone.[20]

In PMMs, BRAF mutation is rare and evidence for the efficacy of C-Kit targeted therapy and BRAF therapy as monotherapy and in combination with MEK-inhibition has not been proven, unlike for CM.[13]

According to the UK guidelines for patients with advanced PMM of the head and neck, combination immunotherapy (anti-PD1 and anti-CTLA-4) should be prescribed if patients are fit and willing to accept immune-related adverse events.[13] Single-molecule immunotherapy (anti-PD1 or anti-CTLA-4) can be considered for reduced toxicity in comparison to combination immunotherapy.[13] In case of failure of immunotherapy, BRAF or C-KIT targeted therapies should be offered for patients with appropriate mutations.[13] If immunotherapy and targeted therapy are not options or have been exhausted, chemotherapy can be considered.[13]

Compared to other tumors, PMMs are characterized by aggressive behavior and less favorable prognosis.[3]

They also seem to be more aggressive than CM, probably due to the delayed diagnosis, the rich lymphatic and vascular supply of the mucosa, and a more aggressive biology.[3,5]

They have a high tendency to relapse, regardless of the radicality of resection and adjuvant treatments administered.[1,2]

The 5-year overall survivor in PMMs is <30% in most series.[1]

Among our patients, there was a case of lymph node metastasis and a case of distant metastasis. After treatment, one patient had local recurrence. A local and distant recurrence was noted in one case. Two patients died of their cancer.

Amelanotic melanomas, advanced T-stage, positive surgical margins, deep infiltration, male gender, vascular invasion, high Ki67 score, and distant metastasis have frequently been associated with poorer prognosis.[2] Compared to OMMs, SNMMs have a better prognosis.[21] However, the main prognostic factor remains the extent of the primary tumor.[1]

As for the treatment and prognosis of PSGMs, because these tumors are extremely rare, there is limited research and data available on their treatment and prognosis. Up until October 2023, there may be case reports and small studies, but comprehensive large-scale studies on this specific type of melanoma are not available. However, the approach for treating these tumors reported in the literature is usually similar to that of PMMs.

Conclusion

Similarly to CM, primary non-CM are highly aggressive tumors with a high risk of relapse. The prognosis of these tumors is poor due to their delayed diagnosis, aggressive behavior, and due to its tendency to develop distant metastases.

In PMMs, the 5-year overall survival is <30% in most series. Surgery is the treatment of choice. The need for a lymph node dissection remains controversial because of the low incidence of lymph node metastases.

Metastatic forms can require systemic treatments such as immunotherapy, targeted therapies, and chemotherapy. As for radiotherapy, a good response has been demonstrated through some studies. Therefore, it could be performed in locally advanced tumors and for metastatic lymph nodes.

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Author contributions

W.T., C.Z. Data collection; W.T., C.Z. Writing. All authors reviewed the manuscript.

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Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written Informed Consent was obtained from the legally authorized representative of the deceased subject (Cases 1 and 2) and from subject themselves (Cases 3, 4, and 5) for the publication of the case series.

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