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Occult Primary Tonsillar Melanoma Presenting With Multiple Haemorrhagic Brain Metastases

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Abstract

Primary tonsillar melanoma is an exceptionally rare subtype of mucosal melanoma with an aggressive clinical course and poor prognosis. We report the case of a 62-year-old woman presenting with symptoms of raised intracranial pressure secondary to multiple haemorrhagic brain metastases. Initial CT and MRIdemonstratedmultiple haemorrhagic brain metastases highly suggestive of melanoma; however, extensive investigation including CT of the neck, chest, abdomen and pelvis, dermatological examination and thyroid assessmentfailed toidentifya primary lesion. PET-CTsubsequentlydemonstratedincreased uptake within the left palatine tonsil, and biopsy confirmed primary mucosal melanoma harbouring a BRAF V600 mutation. The patient underwent whole-brain radiotherapy followed by combination immunotherapy with ipilimumab and nivolumab. This case highlights the diagnostic challenges posed by occult mucosal melanoma and emphasises the importance of PET-CT inidentifyingrare primary sites.

Categories: Otolaryngology, Oncology, Internal Medicine
Keywords: cancer immunotherapy, mucosal melanoma metastasis, oncology imaging, primary palatine tonsil melanoma, raised intracranial pressure

Introduction

Mucosal melanoma is a rare and biologically aggressive malignancy arising from melanocytes within mucosal membranes, accounting for less than 2% of all melanomas. Approximately half of these tumours occur within the head and neck, most commonly involving the nasal cavity, paranasal sinuses and oral cavity. Primary melanoma of the palatine tonsil is exceptionally uncommon, with fewer than 30 cases reported in the English-language literature [1], and is associated with an aggressive clinical course and poor prognosis due to delayed diagnosis and early metastatic spread [2].

Unlike cutaneous melanoma, mucosal melanoma has no established association with ultraviolet radiation exposure and often presents with non-specific symptoms such as dysphagia, odynophagia, oral bleeding or a visible tonsillar mass. In some patients, however, the primary lesion remains clinically occult, creating a significant diagnostic challenge, particularly when metastatic disease is the initial manifestation. Melanoma has a marked propensity to metastasise to the central nervous system, and haemorrhagic brain metastases are a recognised radiological feature. Nevertheless, presentation with symptomatic intracranial metastases from an occult primary tonsillar melanoma is exceedingly rare.

We present the case of a 62-year-old woman who presented with multiple haemorrhagic brain metastases without an identifiable primary lesion on conventional cross-sectional imaging. The primary tumour was ultimately localised by positron emission tomography-computed tomography (PET-CT) to the palatine tonsil and confirmed histologically as BRAF V600-mutant mucosal melanoma. This case highlights the diagnostic value of PET-CT in melanoma of unknown primary and illustrates the importance of considering rare mucosal sites when routine investigations fail to identify the origin of metastatic melanoma.

Case Presentation

A 62-year-old female presented to casualty with a three-week history of progressive frontal headache, which isexacerbatedby lying flat. This was associated with nausea, several episodes of vomiting prior to presentation and an episode of loss of consciousness. She denied associated fever, neckstiffnessor photophobia.Past medical history in 2018 included splenectomy for infarcted littoral cell angioma. She was functionally independent and had a 40-pack-year smoking history.

At the time of presentation, her clinical examination was remarkable for reduced arm swing on the right side with truncal ataxia. She was also noted to have difficulty with tandem gait and a tendency to lean to the right side. Muscle power was intact, and sensation to pain,fine touchand proprioception was preserved. Cranial nerve examination was unremarkable.

Initial blood investigations, summarised in Table *1*, showed an elevated white cell count, predominantly

neutrophils and a normal haemoglobin.

Investigation	Result	Normal range
Total white cell count	13.13 ×10⁹/L	4.3-11.4 ×10⁹/L
Haemoglobin	15.2 g/dL	12.0-15.5 g/dL
C-reactive protein	5.5 mg/L	0-5 mg/L
Urea	3.50 mmol/L	1.7-8.3 mmol/L
Creatinine	53 µmol/L	45-84 µmol/L
Sodium	140 mmol/L	135-145 mmol/L
Potassium	5.31 mmol/L	3.5-5.1 mmol/L

TABLE 1: Summary of preliminary blood investigations taken on admission.

A non-contrast brain CT was performed, which showed multiple solid hyperdense nodules in the parenchyma, somedemonstratingextensive surrounding oedema. The largest lesion was in the right occipital and temporal lobes, measuring up to 2.2 cm in diameter (Figure *1*). To complete staging given the brain CT findings, a CT scan of the neck and trunk was performed, which did not show any signs of primary malignancy.

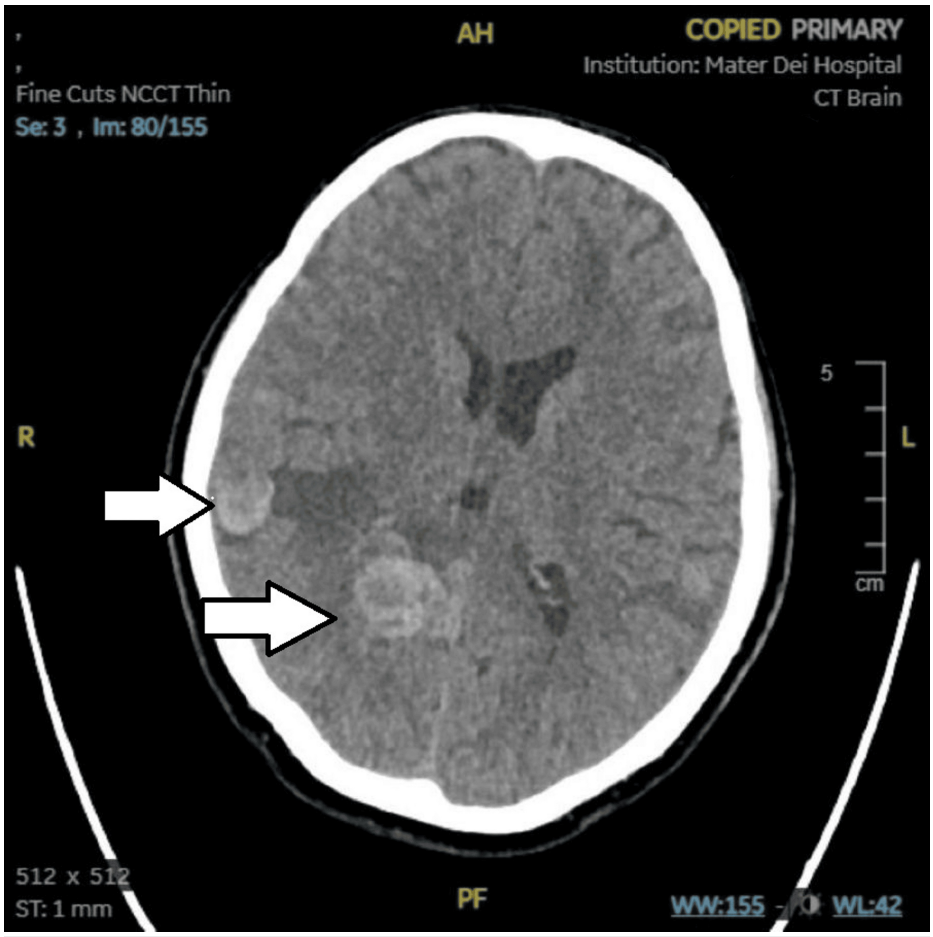


FIGURE 1: Unenhanced brain CT showing two metastatic deposits in the right temporal and parietal lobes with surrounding oedema.

Following consultation with the neurosurgical team, the patient was started on intravenous dexamethasone

4 mg every eight hours with proton pump inhibitor cover. A head MR was also performed to characterise the brain CT findings further. Thisdemonstratedthree haemorrhagic intra-axial lesions in both cerebral hemispheres (Figure 2), which demonstrated a T1 hyperintense signal. Gradient-echo sequences showed susceptibility artefact consistent with the presence of blood products and/or melanin. The imaging appearances were considered highly suggestive of haemorrhagic metastatic disease. At this stage, the leading differentials included metastatic melanoma, renal cell carcinoma, thyroidcarcinomaor haemorrhagic metastases from lung carcinoma; however, the lesions described above were not biopsied.

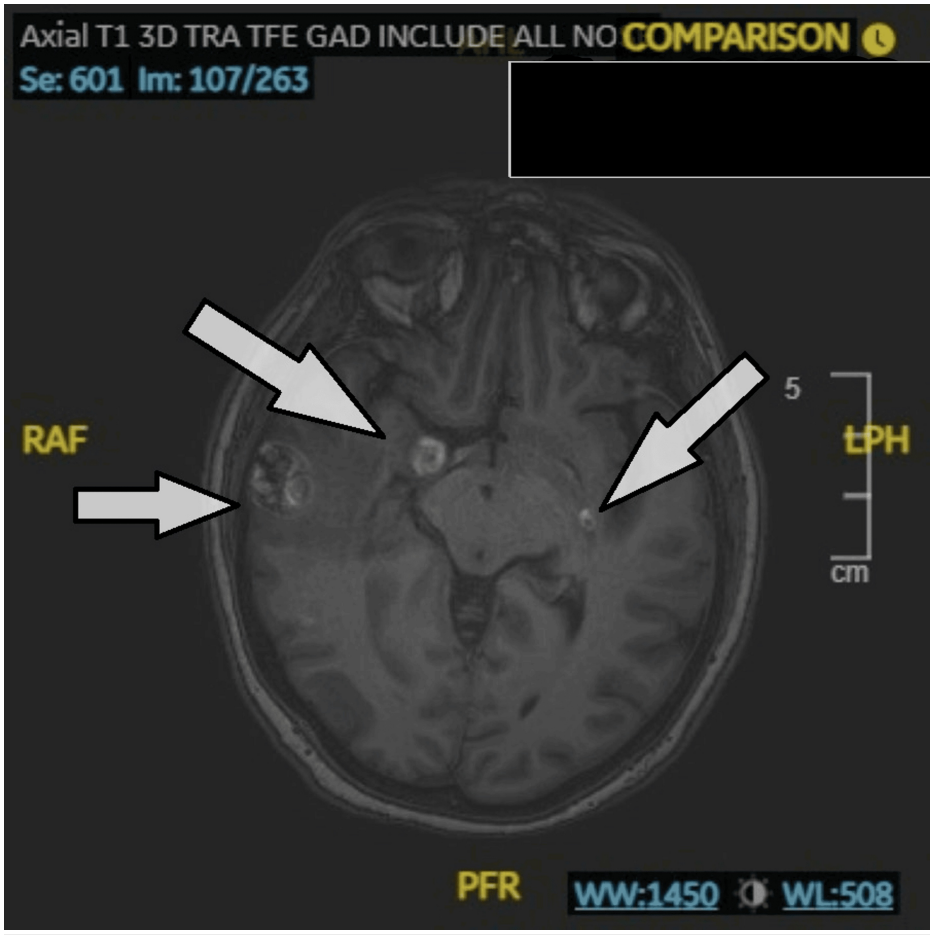


FIGURE 2: Head MR showing intra-axial metastatic deposits that are high signal intensity on T1 imaging.

Subsequentinvestigations were therefore targeted towards these primaries. Given the normal findings on CT scan of the neck and trunk, renal cell and lung carcinoma were highly unlikely. A dermatology review was performed, including extensivedermoscopicassessment; however, no suspicious superficial skin lesions wereidentified. A targeted ultrasound assessment of the thyroid was also performed, which showed a multinodular goitre; no suspicious lesions wereidentified.

In view of the unclear diagnosis with regard to the underlying primary lesion, a consultation with oncology was performed, whichadvisedperforming a PET-CT. After three weeks, a PET-CT was performed, whichdemonstratedfocal fluorodeoxyglucose (FDG) uptake within the left palatine tonsil (Figure 3) despite the absence of a corresponding structural abnormality on contrast-enhanced CT. There were no other FDG-avid sites found during the study. Considering that there was no other clinically identifiable reason for inflammatory tonsillar uptake on PET-CT, such as recent tonsillitis, pharyngitis or recent dental infections, coupled with the paucity of sites amenable to biopsy, these findings prompted a targeted biopsy, whichestablishedthe diagnosis of primary mucosal melanoma.Given the multiplicity and radiological appearance of the intracranial lesions together with the identification of an accessible PET-avid tonsillar lesion, tissue diagnosis was obtained from the tonsil rather than the brain.Histology revealed fragments of ulcerated squamous-lined mucosacontainingmalignant mucosal melanoma with both junctional and invasive components. The neoplastic cells show strong immunoreactivity for S100, Melan-A and SOX10. The tissue specimen was sent for molecular genetic analysis, and a V600E mutation in the BRAF gene was found in this specimen. Following histological confirmation of tonsillar melanoma, the patient was urgently referred to oncologists and given whole-brain radiotherapy delivering 20 Gy in 5 Fr, followed by ipilimumab

(3mg/kg) and nivolumab (1 mg/kg) every three weeks for four cycles. Whole-brain radiotherapy was selected instead of stereotactic treatment due to the severe extent of intracranial involvement and size of the metastatic lesions. Immunotherapy was chosen over BRAF-targeted therapy as the patient had a performance status of 1, had generally well-controlled symptoms, and the target of treatment was to attempt to achieve long-term control of the disease. Following two cycles of immunotherapy, the patient developed transient bilateral lower limb weakness; however, repeat brain CT did not show any new metastatic lesions. Following the fourth cycle of immunotherapy, her performance status declined to 3, and she presented with pleuritic left-sided chest pain. Pulmonary artery CT showed extensive bilateral pulmonary emboli, more pronounced on the left, involving the central, lobar and segmental pulmonary arterial branches. The patient died of respiratory failure secondary to pulmonary embolism, likely as a complication of reduced mobility and metastatic malignancy, within three months of initial diagnosis.

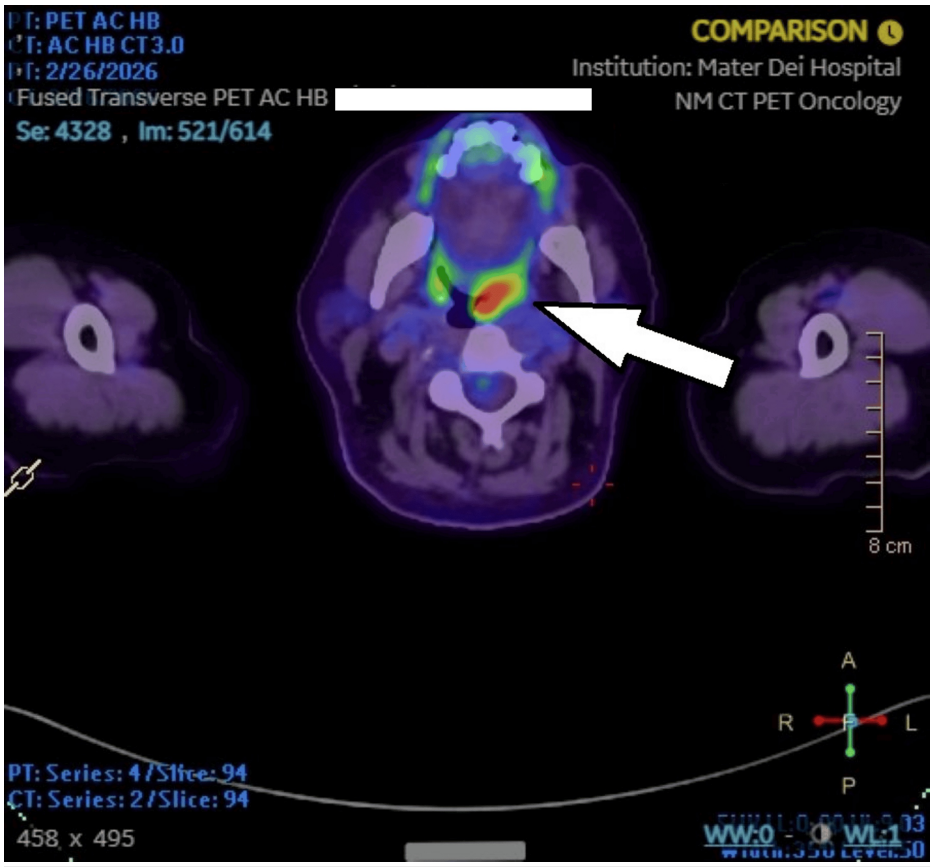


FIGURE 3: PET-CT showing increased asymmetrical uptake in the left palatine tonsil.

Discussion

Primary mucosal melanoma of the palatine tonsil is an exceptionally rare malignancy,representingone of the rarest subtypes of head and neck mucosal melanoma [1]. While mucosal melanomas account for less than 2% of all melanomas,approximately halfoccur within the head and neck region [3]. The most common sites include the nasal cavity, paranasal sinuses, and oral cavity; involvement of the palatine tonsil is exceedingly uncommon [1,3]. The rarity of this disease has limited the available evidence to isolated case reports and small case series [1,4,5].

The first documented case was reported in the 1950s, and since then, fewer than 30 primary tonsillar melanomas have been described in the English-language literature. A comprehensive review published in 2017identified26 reported cases dating back to 1910, while asubsequentreview in 2022 increased this number to 27 reported cases before presenting anadditionalpatient[1,4].

Most patients are diagnosed in the sixth to eighth decades of life, although younger patients have been reported. Mucosal melanomas are very commonly asymptomatic and very often remain silent until the disease is advanced. Clinical manifestations, when present, are nonspecific and commonly include dysphagia, odynophagia, sore throat, foreign-body sensation, oral bleeding, or an enlarging tonsillar mass. Cervical lymphadenopathy isfrequentlythe presenting feature because regional nodal metastases are common at diagnosis [3,5]. Unlike cutaneous melanoma, mucosal melanoma lacks well-established

environmental risk factors such as ultraviolet radiation exposure. Lesions are mostly found on the hard palate or the alveolar ridge. Rarer locations include the lips, buccal mucosa, floor of mouth and tonsils. In up to 35% of cases, the lesions are amelanotic and can appear similar in colour to the mucosa, making the diagnosis more difficult.

Compared to other melanomas, mucosal melanomas have the lowest five-year survival rate,likely due todelayed detection and diagnosis. Oral mucosal melanoma is characterised by rapid progression and a tendency to metastasise early. The most common sites for metastasis include the liver,lungsand the central nervous system. Melanoma has one of the highest propensities among solid tumours to metastasise to the brain [6]. Intracranial metastasesfrequentlydemonstratespontaneous haemorrhage because of tumour neovascularisation and vascular fragility. On MRI, melanin and blood products may both contribute to intrinsic T1 hyperintensity and susceptibility artefact, findings that should prompt consideration of metastatic melanoma in theappropriate clinicalsetting.

Prognosis of oral mucosal melanomas is highly dependent on the stage of disease, staged using the American Joint Committee on Cancer (AJCC) system [7]. Unlike most other malignancies, mucosal melanomas of the head and neck are staged beginning at T3 because all lesions are considered biologically aggressive. T3 disease is limited to the mucosa andimmediatelyunderlying soft tissue, while T4a and T4b describe progressively advanced local invasion. Distant metastatic disease, asobservedin this case, is classified separately as M1 disease and is associated with a particularly poor prognosis, with prognosis often measured in months.

Oral mucosal melanoma can be divided histologically into epithelioid, spindle, plasmacytoid or mixed types. Histopathology is essential to distinguish oral mucosal melanoma from other oral neoplasms. To differentiate, immunohistochemical markers, such as S100, Melan-A and SOX-10, are used as markers for diagnosis of primary oral mucosal melanoma, as shown in Figures *4*-*6*, respectively [3,8]. SOX10 is now considered one of the most sensitive melanocytic markers and is routinely used alongside S100, Melan-A and HMB45.

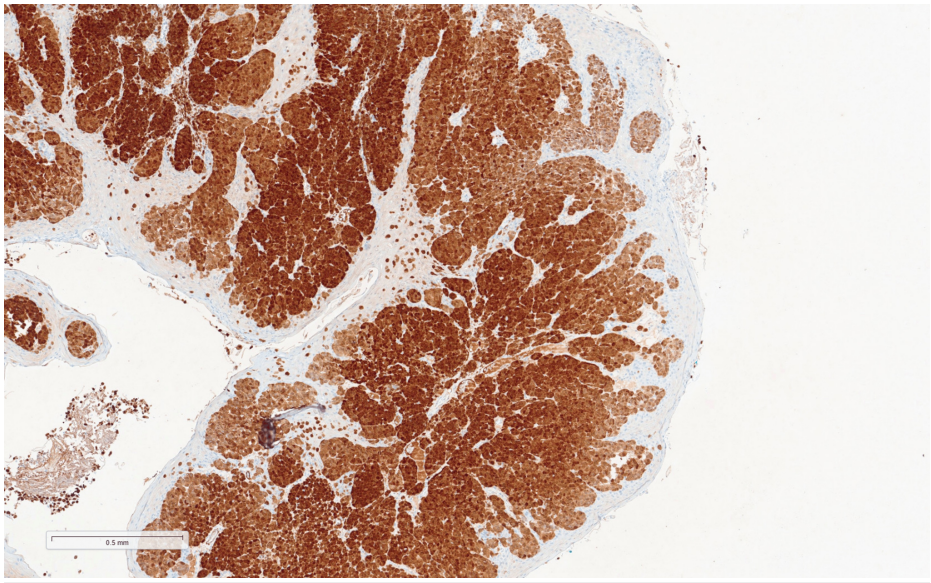


FIGURE 4: Immunohistochemical staining demonstrating diffuse cytoplasmic and nuclear positivity for S100 in tumour cells at ×5 magnification, in keeping with melanocytic differentiation.

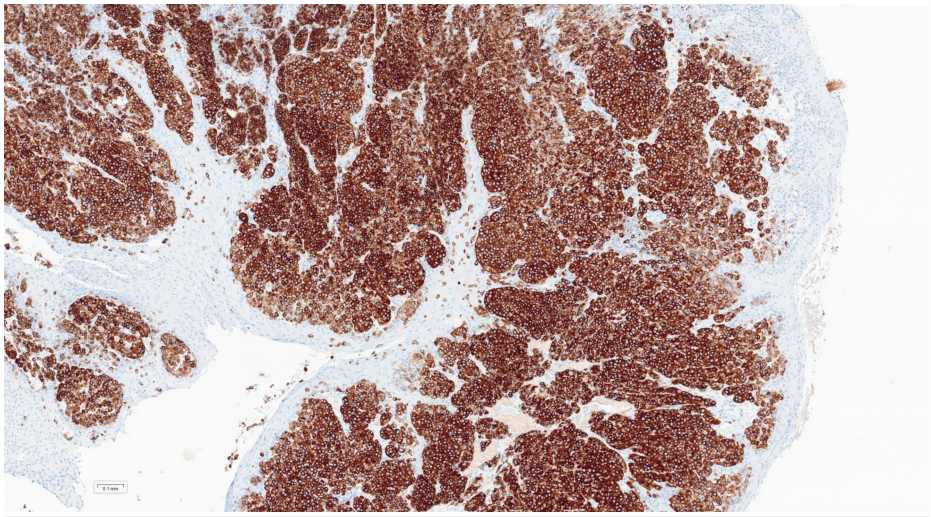


FIGURE 5: Immunohistochemical staining demonstrating diffuse cytoplasmic positivity for Melan-A in tumour cells at ×5 magnification, in keeping with melanocytic differentiation.

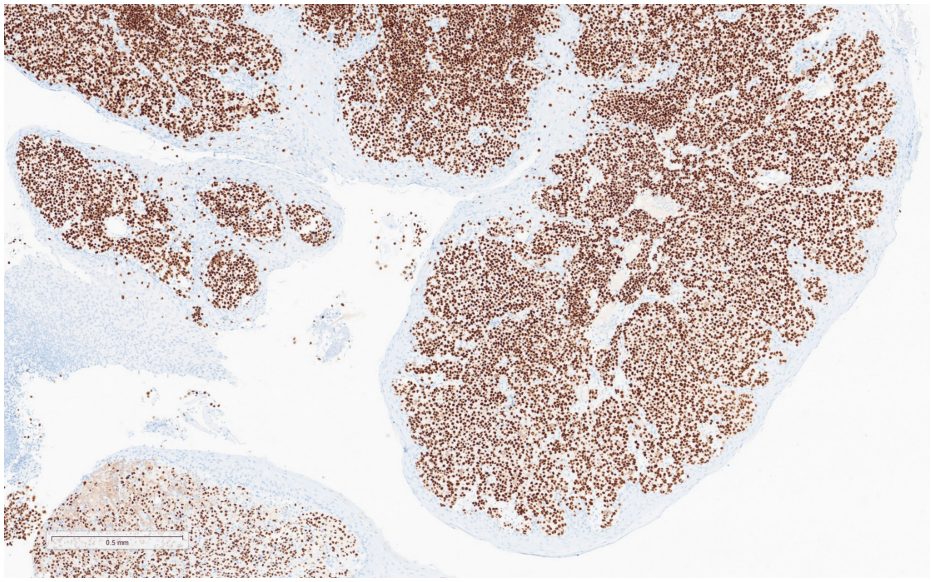


FIGURE 6: Immunohistochemical staining demonstrating strong, diffuse nuclear positivity for SOX-10 in tumour cells at ×5 magnification, in keeping with melanocytic differentiation.

Mucosal melanoma is a biologically distinct subtype of melanoma, compared with cutaneous melanoma; mucosal melanomas generally have a lower tumour mutational burden. Cutaneous melanomas, particularly those associated with chronic ultraviolet exposure, often harbour a high number of UV-signature mutations, particularly involving BRAF, NRAS and NF1. In contrast, mucosal melanomas lack these typical UV-signature mutations and instead demonstrate structural genomic alterations such as mutations involving KIT and SF3B1.

Approximately 40-50% of cutaneous melanomas harbour activating BRAF mutations; however, these mutations areconsiderably lesscommon in mucosal melanoma, occurring inapproximately 3-15% of cases [9].In BRAF-mutated melanomas, BRAF becomes hyperactivated, resulting in increased cell proliferation and survival. The most common is the V600E mutation, which accounts for 80-90% of BRAF mutations in melanomas and is present in almost 60% of cutaneous cases but is present in only 5% of mucosal melanomas, highlighting another rare feature in this case presentation. The mutated gene leads to the production of a constitutively activated BRAF protein that dysregulates downstream MAPK signalling, promoting cellular proliferation and inhibiting apoptosis. They also create an immunosuppressive

environment, preventing presentation of tumour antigens by dendritic cells and macrophages. The BRAF inhibitors vemurafenib, dabrafenib andencorafenibare approved for use in the treatment of patients with BRAF V600 mutant advanced melanoma [9].

In this case, given the presence of multiple symptomatic brain metastases, whole-brain radiotherapy was administered with the aim of achieving rapid control of intracranial disease. Following identification of a BRAF V600 mutation, systemic treatment options were discussed, and combination immune checkpoint inhibition with ipilimumab and nivolumab wasinitiated. Cancer cellscanevade immunosurveillance and downregulate adaptive immunity during tumour growth by activating immunosuppressive signals or immune checkpoints on T cells such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death-1 (PD-1). CTLA-4 and PD-1 are inhibited by ipilimumab and nivolumab, respectively, thereby reversing inhibition of T-cell function and increasing anti-tumour immunity [10]. Combination immune checkpoint inhibition hasdemonstrateddurable systemic and intracranial responses in patients with metastatic melanoma, including those with brain metastases. While BRAF-targeted therapies can induce rapid tumour regression, responses are often limited by the development ofacquiredresistance. The presence of a BRAF V600 would havehypothetically beenclinically significant, as itprovideda potential therapeutic optionin the event ofdisease progression despite immunotherapy.

Conclusions

To our knowledge and after review of the available English-language literature,presentation with symptomatic haemorrhagic brain metastases from an occult primary tonsillar melanoma appears to be exceptionally rare. Unlike most reported cases, which present with dysphagia, odynophagia or a visible tonsillar mass, our patient had no local oropharyngeal symptoms, and the primary lesion remained occult on conventional CT imaging. This case alsodemonstratesthe complementary role of PET-CT in patients with metastatic melanoma of unknown primary. Although CT of the neckfailed toidentifya structural abnormality, PET-CTdemonstratedmetabolically active disease within the tonsil,ultimately directingbiopsy andestablishingthe diagnosis.This casedemonstratesthat PET-CT can play a pivotal role inidentifyingoccult mucosal primaries in patients presenting with metastatic melanoma of unknown origin and should be considered when conventional cross-sectional imagingfails toidentifya primary lesion.

To conclude, the main learning points from this case report are that multiple haemorrhagic brain metastases should raise suspicion for metastatic melanoma. Negative CT imaging does not exclude an occult mucosal primary, and PET-CT may identify metabolically active lesions that are morphologically occult.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Nicholas Tabone Adami, Chantal Vella, Michelle Ann Ceci

Acquisition, analysis, or interpretation of data: Nicholas Tabone Adami, Ishana Chatlani, Thelma Xerri, Chantal Vella, Michelle Ann Ceci

Drafting of the manuscript: Nicholas Tabone Adami, Ishana Chatlani, Thelma Xerri, Michelle Ann Ceci

Critical review of the manuscript for important intellectual content: Thelma Xerri, Chantal Vella, Michelle Ann Ceci

Supervision: Chantal Vella

Disclosures

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