



Case report

Metastatic malignant melanoma of unknown primary site to the brain: A case report

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ABSTRACT

Introduction and importance: The natural history of metastatic melanoma in the absence of a known primary site has been poorly defined. The disease usually presents a significant cause of morbidity and mortality. Around 90% of melanomas have cutaneous origin, but still there are melanomas that could be found in visceral organs or lymph nodes with unknown primary site. Spontaneous regression of the primary site could be an explanation. The disease is frequently diagnosed after treatment for known extracranial metastases and has a poor outcome despite various local and systemic therapeutic approaches.

Case presentation: Herein, we present a case of a 43-year old female presented with history of headaches and enlarged a left inguinal lymph node. Notably, no cutaneous lesions could be identified by history or on physical examination. CT-scan of the brain revealed a space occupying lesion and the inguinal lymph node biopsy confirmed the diagnosis of metastatic malignant melanoma. The patient succumbed shortly after establishment of diagnosis.

Clinical discussion: Most patients with brain metastases from malignant melanoma are diagnosed after treatment for known extracranial metastases and have a poor outcome despite various local and systemic therapeutic approaches.

Conclusion: Metastatic melanomas of brain with unknown primary present a significant morbidity and mortality and confer a poor prognosis. Delay in diagnosis and treatment is of serious concern when it comes to improve the prognosis of patients with this disease. The optimal treatment depends on the objective situation, often surgery, radiosurgery, whole brain radiotherapy and chemotherapy can be used in combination to obtain longer remissions and optimal symptom relieve.

1. Introduction

The vast majority of malignant melanoma (MM) have an apparent cutaneous primary lesion [1]; but sometimes they may present metastatically in the absence of a primary lesion – so-called melanomas of unknown primary origin [2–3]. Metastases to the brain far outnumber primary brain tumors. The most common sources of brain metastases are lung cancer, breast cancer, and melanoma. While lung cancer and breast cancer are much more prevalent, melanoma has the highest risk of spread to the CNS among all common cancer types. Previous studies have demonstrated that 40–60% of patients with metastatic melanoma develop brain metastases at some point in the course of their disease,

and autopsy series identified CNS involvement in up to 80% of patients with metastatic melanoma [4]. These metastases usually develop late in the course of the disease. Only 7% of patients had brain metastases disclosed at the time of initial diagnosis [2]. It is uncommon that melanoma patients with brain metastases continue to have an occult primary tumor after initial thorough work-up and staging [3–4].

Herein we present an uncommon presentation of MM in a case of a middle-aged female patient who presented to the outpatient clinic of Kilimanjaro Christian Medical Centre (KCMC); complaining of severe headaches for three weeks. KCMC is a tertiary referral and academic center in Northern Tanzania. CT-scan of the brain revealed a space occupying lesion while an inguinal lymph node biopsy confirmed the

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diagnosis of metastatic MM. This work has been reported in line with the SCARE 2020 criteria [5].

2. Presentation of case

A 43-year-old African female, a self-referral patient presented to our center because of severe headache. The headache was periodic and it was throbbing in nature; localized on the bilateral temporal and frontal areas. It was occurring approximately 2 hourly. The pain was relieved by closing eyes, sponging and use of Diclofenac injection. She also reported a history of tonic-clonic convulsions for one week that lasted for about two minutes and was associated with urine incontinence. She had no visual disturbances, no loss of consciousness, no confusion neither behavioral changes. Her past medical history was non-significant, and has been smoking for nearly 20 years. She was a house wife with small scale business.

On general examination she was fully alert and awake with a Glasgow coma scale of 15/15, her memory was intact and had no focal neurological deficit noted. A nodular swelling on her left inguinal area measuring about 8x6cm, slightly tender and hard was noted. It had an intact overlying skin with no redness or discharging tract. A thorough attempt to search for the primary site on the lower limbs was uneventful. The patient did not remember exactly when the swelling started but approximately over months. Review of other systems including genital examination and digital rectal examination were completely negative. Her vital signs and blood work were essentially unremarkable except for neutrophilia of 73.7%. The ultrasound of the left thigh was suggestive of a groin mass with cystic changes. Chest/abdomen CT-scan showed no evidence of primary tumor. Presence of a solitary hepatic metastasis and large necrotic superficial left femoral lymph nodes was noted, (Fig. 1). Brain CT-scan was done and showed hyperdense lesions on the right hemisphere with vasogenic edema around it and another similar lesion on the left occipital lobe (Fig. 2). Our first impression was a secondary malignant neoplasm of the brain and cerebral meninges.

A team of experienced surgeons scheduled a surgical procedure where an excision biopsy of the groin mass was performed under general anesthesia. Intra-operatively, the mass of about 8 × 6 cm, black colored with smooth margins and no extension to the surroundings was noted. The mass was excised and taken for histopathology evaluation. The histopathology report highlighted a lymph node with near complete effacement of the nodal architecture and replaced by a diffuse tumor whose cells were hyperchromatic, epithelioid and spindle shaped. Frequent mitoses, necrosis and the presence of brown pigmentation were associated, (Fig. 3). In addition, the tumor cells were immune

reactive with HMB-45 immunostaining thus confirming the diagnosis of metastatic MM of unknown primary, (Fig. 4).

The patient was kept on dexamethasone, phenytoin, diclofenac and antibiotics which relieved her symptoms. She was discharged on 7th day after operation and was instructed to return after 4 weeks for oncological treatment. However, the patient did not show up on her appointment. It was later found via telephone call that unfortunately the patient succumbed few days post hospital charge.

3. Discussion

MM is an aggressive malignancy with an increasing incidence worldwide. It has been noted that MM has a high risk for dissemination, both through lymphatic and hematogenous pathways [1–2]. Usually, the primary tumor can be detected on the skin, mucosa, or ocular tissue and is classified as MM of known primary. However, it may also present without known primary tumor, called MM of unknown primary [2]. It is estimated that 2–6% of all melanoma patients have unknown primary tumor [3]. The pathogenesis of metastatic brain MM with unknown primary is still not fully understood. Hypothetically, unknown primary MM is suggested to arise from primary MM that has spontaneously regressed and cannot be detected [6]. Other hypotheses suggest that ectopic nevus cells residing in visceral organs, lymph nodes, or the nervous system may also give rise to MM. Finally, the patient may have had the formation removed without histological diagnosis or the formation might have been misdiagnosed [6]. In cases of recurrence, re-biopsy has been described as a successful approach to suggest the origin of cancer and elucidate possible therapeutic approaches.

MM brain metastasis is the disease which is yet to be fully understood, because there are only theoretical assumptions about the nature of the disease. It has many severe side effects and, unfortunately, any disease related to the brain has limited therapeutic options due to the blood-brain barrier [7]. The course of the disease after a treatment course is complicated to predict, and it is difficult to obtain long-lasting remission [8]. In this report, we describe a female patient with unknown primary melanoma brain metastasis. Unfortunately, our patient expired prior to oncologic treatment.

In the study by Fife and coworkers, the median expected overall survival from the time of diagnosis is approximately 5 months [9]. The course of disease is typically characterized by rapid extracranial progression and short overall survival time despite various local and systemic treatment approaches. Here the authors discussed an unusual case where a patient presented with a brain metastasis as the first symptom of disease, a presumed primary in the gastro-intestinal tract and favorable



Fig. 1. Axial CT pelvis showing an enlarged matted and necrotic lymph nodes in the left superficial femoral region suggestive of metastatic lymphadenopathy.

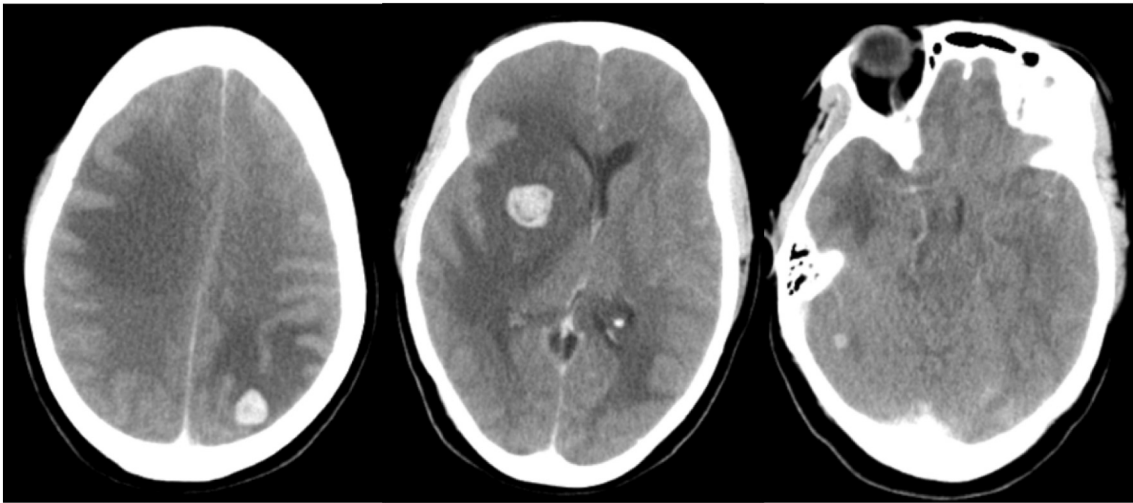


Fig. 2. Axial CT brain shows three hyperdense masses in the right lentiform nucleus (1.8 cm × 1.6 cm), left parietal lobe (1.5 cm × 1.1 cm) and left occipital lobe (1.7 cm × 1.7 cm) with surrounding perilesional oedema; effacement of the right lateral ventricle seen with 0.6 cm midline shift towards the left side the features suggestive cerebral metastasis.

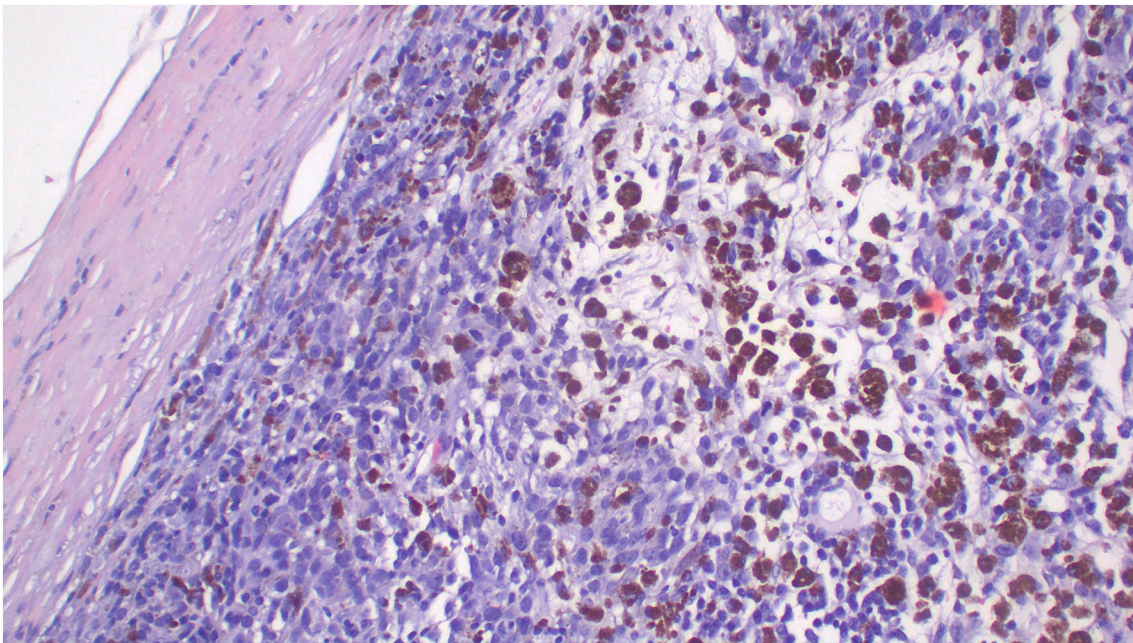


Fig. 3. Histopathology of the inguinal lymph node demonstrating a complete effacement of the nodal architecture and replaced by a tumor whose cells were hyperchromatic, epithelioid and spindled shaped and the presence of brown pigmentation, H & E staining, ×100 original magnification. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

survival and disease-control in the absence of any systemic therapy. The brain is a favorable environment for the development of metastases due to processes like migration, proliferation, and angiogenesis [10]. MM brain metastases are associated with complications like hemorrhage, increased intracranial pressure, and focal or generalized seizures. To achieve a favorable disease course, it is necessary to consider multi-modality treatment strategies [11].

Our patient represents an example of MM with unknown primary. The current literature suggests that about 2–3% of all MM patients present with a metastasis without a detectable primary tumor [12]. The previously noted clinical and histologic observations made during the previous three decades support the disappearance of a primary lesion as a result of spontaneous regression, which still remains a plausible explanation for MM with unknown primary [13]. As it was the case in

our patient, most brain MM metastases present with headaches. The symptoms are due to increased intracranial pressure, mass effect, impaired cerebrospinal fluid drainage and focal deficits. Moreover, weakness, numbness, imbalance, and visual loss, behavioral changes related to particular brain regions as well as seizures are also common [14]. Given the recognized neurotropism of melanoma, neurological symptoms in a melanoma patient should prompt diagnostic imaging studies. Asymptomatic metastases are increasingly diagnosed through increased screening due to known risk factors as well as mandatory imaging required during screening for many melanoma clinical trials [15–16]. About 80% of brain metastases are supratentorial, while 15% are infratentorial or leptomeningeal, and 5% affect the brainstem itself. CT scans of the brain with and without contrast can detect most metastases ≥ 10 mm in the supratentorial region and most hemorrhagic

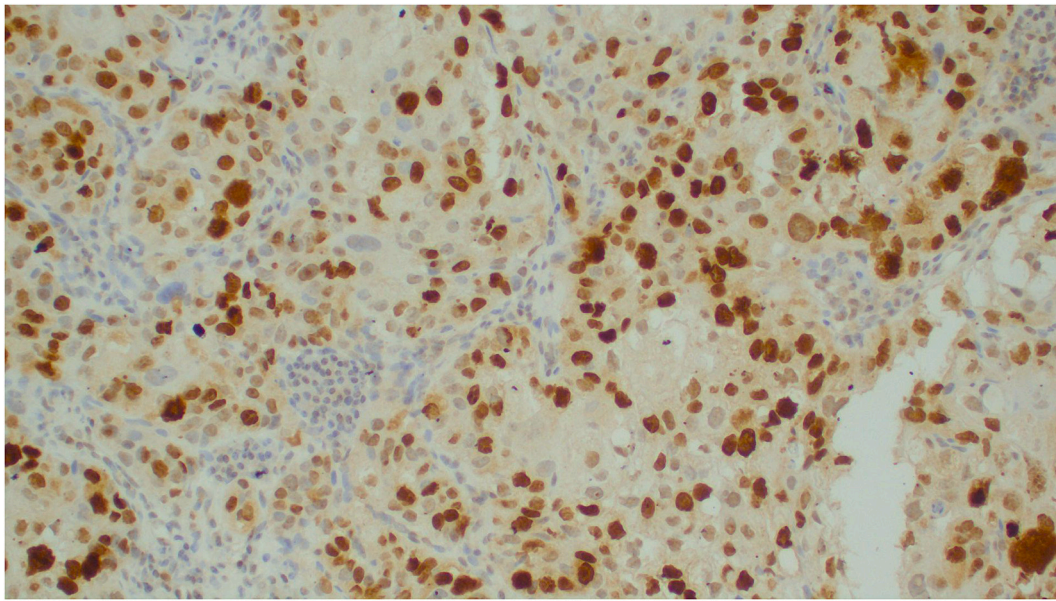


Fig. 4. Photomicroscopy demonstrating strong immune reactive of the tumor cells with HMB-45, IHC $\times 200$ original magnification.

lesions [17]. However, magnetic resonance imaging (MRI) with and without gadolinium is far more sensitive, particularly for smaller lesions, lesions in the posterior fossa, and lepto meningeal disease. MM metastases are typically enhancing and are frequently associated with hemorrhage and edema [13]. Nearly 37% of patients with stage IV melanoma eventually develop clinically apparent brain metastasis, and autopsy series report the prevalence of brain metastasis at 55% to 75% of patients who died of melanoma [13]. Risk factors associated with melanoma brain metastasis include male gender, mucosal or head and neck primaries, thick or ulcerated neoplasms, acral lentiginous or nodal lesions, and stage IV disease [7]. Brain metastasis typically occurs relatively late in the course of melanoma — a median interval of 2.2 to 3.8 years after the diagnosis of the primary disease [16]. Patients with a single lesion and an absence of extracranial metastasis who initially present with brain metastasis have a better prognosis.

The current management strategies appear unsatisfactory and brain metastasis contributes to death in nearly 95% of patients, with a median survival of less than 1 year despite treatment [7]. This is partly due the blood-brain barrier which limits the access of circulating molecules from entering the brain parenchyma; therefore, the use of traditional cytotoxic chemotherapy is limited [18]. Moreover, there has been little improvement in the prognosis of brain metastasis due to MM during the last 3 decades; thus, patients with this disease are usually excluded from melanoma clinical trials. However, new approaches appear to offer new hope to selective patients. The usually prescribed treatments for brain metastases are surgery and/or radiation therapy [19]. For patients with advanced-stage melanoma, BRAF-targeted regimens and immunotherapy have shown some efficacy improving the overall survival. It has been suggested that BRAF-targeted regimens might show efficacy in patients with brain metastases [20].

4. Conclusion

MM may present metastatically without an identifiable primary lesion. Melanoma brain metastases cause significant morbidity and mortality and confer a poor prognosis. The optimal treatment of MM patients with CNS metastases depends on the objective situation, often surgery, radiosurgery, whole brain radiotherapy and chemotherapy can be used in combination to obtain longer remissions and optimal symptom relieve. Delay in diagnosis and treatment as it was the case in our patient is of concern when it comes to improve the prognosis of patients

with this disease. Thus, clinicians should have a suspicion of index for unusual cases and thus vigorously work up including proper and timely diagnosis is essential for optimal patient care.

Abbreviations

CNS	central nervous system
CT	computed tomography scans
H&E	hematoxylin and eosin staining
IHC	immunohistochemistry
MM	malignant melanoma
MRI	magnetic resonance imaging

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There was exemption of ethical clearance.

Consent

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Author contributions

All authors made substantial contributions to the paper. AM and JL conceived and planned the study. GG, AM, JL and AS reviewed the patients' medical records, planned and executed management. JL was the lead surgeon. JL prepared the initial manuscript version. AM performed histopathological analysis, critically reviewed the paper and prepared the final manuscript. All authors read and approved the final manuscript.

Research registration

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All authors have declared that no competing interests exist.

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