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(CASE REPORT)

Metastatic malignant melanoma of unknown primary diagnosed by fine needle aspiration cytology: Case report and brief literature review

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Abstract

Melanoma of unknown primary (MUP) is a rare form of metastatic melanoma in which nodal or visceral involvement is identified without an evident cutaneous, ocular, or mucosal primary lesion. We report the case of a 49-year-old man who presented with a gradually enlarging, painless mass in the right posterior cervical neck over three months, without constitutional symptoms or a prior history of melanoma.

Fine-needle aspiration (FNA) of the lymph node revealed dyscohesive, pleomorphic malignant cells characterized by eccentric nuclei, prominent macronucleoli, intranuclear cytoplasmic inclusions, and focal brown cytoplasmic pigment. Immunohistochemical (IHC) analysis of the cell block showed positivity for S-100, SOX10, HMB-45, and Melan-A, with negative staining for epithelial, lymphoid, pulmonary, and squamous markers, supporting a diagnosis of metastatic malignant melanoma. An extensive diagnostic workup, including full-body dermatologic examination, ophthalmologic assessment, otolaryngologic and mucosal evaluation, cystoscopy, proctoscopy, whole-body PET-CT, and brain MRI, did not identify a primary lesion. Molecular testing revealed a BRAF V600E mutation.

The patient underwent a right selective neck dissection, which demonstrated metastatic melanoma in three of seventeen lymph nodes without extranodal extension. He subsequently received adjuvant therapy with dabrafenib and trametinib. Surveillance imaging at six and twelve months showed no evidence of recurrent or new disease.

This case underscores the diagnostic utility of FNA cytology with cell block preparation, along with IHC and molecular testing, in establishing a definitive and clinically actionable diagnosis of metastatic MUP.

Keywords: Melanoma of unknown primary; Melanoma of known primary; Fine-needle aspiration; Immunohistochemistry; BRAF V600E; Multidisciplinary

1. Introduction

Melanoma is a form of skin cancer that originates in melanocytes located in the stratum basale layer of the epidermis. Although it is not the most common skin cancer, it is certainly considered the most aggressive and most deadly skin

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cancer that can metastasize to distant sites, such as the brain, lungs, liver, and other sites. [1] Risk factors for melanoma include prolonged UV radiation exposure, excessive tanning bed usage, and a fair-skinned phenotype. [2,3] It is especially more common among Caucasian men above the age of 65. [2]

Although melanoma primarily arises on the skin surface, it can also occur on mucosal surfaces and ocular structures. Melanomas with metastatic potential usually have a known primary site and are collectively referred to as melanoma of known primary site (MKP). However, a subset of melanomas lacks a primary site, accounting for approximately 3.2% of melanoma cases. [4] This phenomenon is commonly known as melanoma of unknown primary site (MUP), and it is usually present in lymph nodes, subcutaneous tissue, and visceral organs.

A melanoma is typically diagnosed via a biopsy. In cases of MUP, FNA cytological analysis plays an integral role. Additionally, molecular analyses, particularly through the identification of mutations such as BRAF V600E, help further support diagnosis and guide treatment. [5] Treatment for melanoma largely depends on the stage. Surgical excision is the primary treatment for early-stage melanoma, whereas systemic chemotherapy, including immunotherapy and targeted therapy, is the preferred treatment for metastatic melanoma. [6]

In this report, we describe a case of metastatic melanoma presenting solely as lymphadenopathy without an identifiable primary lesion. This case highlights the diagnostic value of cytologic evaluation, the significance of comprehensive workup to exclude a primary source, the role of molecular findings in leading management, and the comparable prognosis of MUP to a stage-matched melanoma with a known primary, potentially reflecting an underlying host immune response leading to regression of the primary tumor.

2. Case Presentation

2.1. Clinical Presentation and Initial Investigations

A 49-year-old man presented to his primary care physician after noticing a gradually enlarging, painless mass along the right side of his neck over a period of approximately three months. He was otherwise well, with no constitutional symptoms, no significant weight loss, and no prior history of skin lesions, moles, or any dermatologic condition treated. His medical history was unremarkable, and he had no family history of melanoma or other cutaneous malignancies. On physical examination, a firm, non-tender lymph node measuring approximately 3.5 centimeters was palpable in the right posterior cervical chain. No other peripheral lymphadenopathy was identified, and the remainder of the examination was unrevealing.

2.2. Fine Needle Aspiration Cytology and Diagnosis

Fine-needle aspiration (FNA) of the node was performed. Multiple passes were performed to ensure adequate cellularity, and a cell block was prepared from the residual material and processed into a paraffin-embedded section for IHC and molecular analysis, alongside the direct smears. Cytology smears revealed a cellular aspiration composed of dyscohesive, pleomorphic cells with eccentric nuclei, prominent macronucleoli, and intranuclear cytoplasmic inclusions, features raising immediate suspicion for melanoma. Some cells harbored finely granular brown cytoplasmic pigment, further supporting the diagnosis. (Figure 1 A, B, C, D)

The cell block confirmed these findings histologically, and IHC studies on the paraffin sections showed strong and diffuse positivity for S-100, SOX10, HMB-45, and Melan-A, with negativity for pan-cytokeratin, TTF-1, CD45, and p63, effectively excluding a carcinomatous, lymphomatous, or squamous primary. The morphologic and immunophenotypic profile was unequivocally that of malignant melanoma.

2.3. Establishing the Diagnosis of Malignant Lymphoma of Unknown Primary

With the diagnosis secured solely on cytology, the clinical imperative shifted immediately to a rigorous search for a primary site. The working diagnosis of melanoma of unknown primary, while well-recognized in the literature, remains one of exclusion, and the thoroughness of that exclusion defines the integrity of the designation.

The patient underwent a meticulous, head-to-toe dermatologic evaluation by an experienced dermatologist using dermoscopy across the entire skin surface, including the scalp, interdigital spaces, subungual regions, and perianal skin. No suspicious lesions, atypical nevi, regressed or scarred areas, or hypopigmented patches suggestive of a spontaneously regressed primary were identified. Ophthalmologic slit-lamp and fundoscopic examinations were performed to assess for uveal or conjunctival melanoma; findings were normal bilaterally. An otolaryngologic evaluation with nasal endoscopy surveyed the nasal cavity, nasopharynx, paranasal sinuses, and the mucosal lining of

the hypopharynx and larynx, all of which were unremarkable. Oral examination with careful inspection of the hard and soft palate, gingiva, buccal mucosa, and tongue revealed no pigmented or ulcerated lesions. Urogenital evaluation included cystoscopic inspection of the bladder mucosa and urethral lining, which was normal, and proctoscopy identified no anorectal mucosal melanoma. Whole-body PET-CT imaging demonstrated intense FDG avidity confined to the right cervical nodal mass with no other site of hypermetabolic uptake in the skin, subcutaneous tissue, viscera, or skeleton. MRI of the brain was clear.

After this systematic and comprehensive workup, no primary site could be identified, and the diagnosis was formally established as metastatic malignant melanoma of unknown primary.

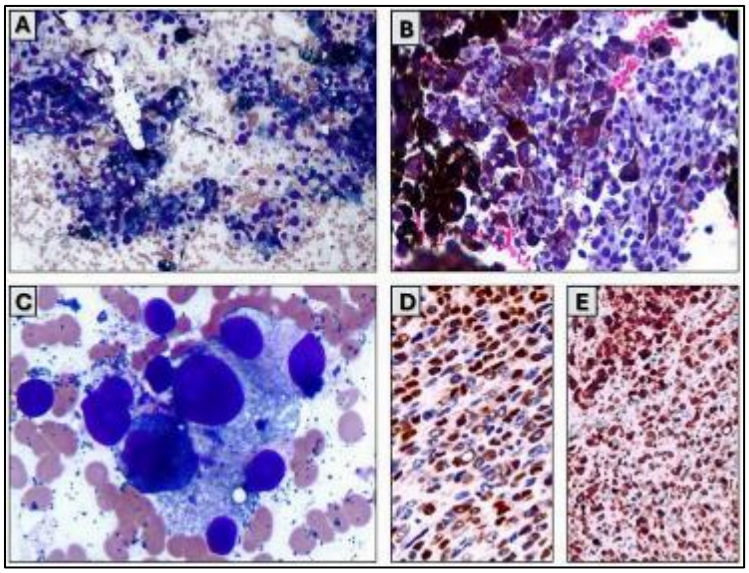
2.4. Multidisciplinary Tumor Board & Management

Molecular analysis of the cell block material was performed in parallel. Next-generation sequencing identified a BRAF V600E mutation, a finding of immediate and significant therapeutic consequence, as it opened the door to targeted therapy in addition to immunotherapy options. The case was presented to the multidisciplinary tumor board, where input was gathered from medical oncology, surgical oncology, radiation oncology, dermatology, and pathology. The tumor board discussion centered on the body of evidence supporting the idea that melanoma of unknown primary, when compared stage-for-stage with melanoma of known primary, carries a comparable or even somewhat more favorable prognosis, a phenomenon attributed in part to the possibility that immune-mediated regression of the primary tumor reflects a host immune response. Given solitary nodal involvement, BRAF mutation, and the patient's good performance status, the board recommended combined-modality treatment.

The patient underwent right-sided selective neck dissection, which yielded a specimen confirming metastatic melanoma in three of the seventeen dissected lymph nodes with no extranodal extension. Adjuvant systemic therapy was initiated with a BRAF and MEK inhibitor combination, dabrafenib and trametinib, given the confirmed V600E mutation, alongside close surveillance imaging and clinical follow-up at regular intervals.

2.5. Follow-Up and Outcome

The patient tolerated treatment well, with manageable side effects. Serial imaging at six and twelve months showed no evidence of recurrent or new disease. He remained in clinical remission at his most recent follow-up, continuing surveillance. His case stands as a reminder that a well-prepared cytology specimen, thoughtfully processed with a cell block and paired with immunohistochemistry and molecular studies, is entirely sufficient to drive a complete and actionable oncologic diagnosis, and that the absence of a known primary, far from being a diagnostic defeat, can be a clinically meaningful finding in its own right.



1A: Cellular smear showing scattered groups and single cells of melanoma cells and melanocytes (FNA, DQ Stain); 1B: Fragments of metastatic melanoma in background of melanocytes (Cell block H&E Stain); 1C: High power view showing melanoma cells with large eccentric nuclei resembling plasma cells (FNA, DQ stain); 1D: Tumor cells Positive for SOX10 (Cell block); 1E: Tumor cells positive for S100 (Cell block)

Figure 1 Fine needle aspiration cytology features and immunohistochemistry studies of metastatic melanoma

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

MUP is a well-known but rare clinical entity, first described in the mid-20th century. This diagnosis implies that metastatic melanoma exists with no detectable identifier of primary origin after extensive investigation. [7] The most widely held hypothesis proposes spontaneous immunomodulated regression of the primary cutaneous tumor, supported by clinical observations showing robust host immune responses in these patients. [8]

MUP makes up 3.2% of melanoma cases globally, and in the majority of cases has nodal spread (especially cervical, axillary, or inguinal) as seen in this case. [4,8,9] Some studies indicate that relatively MUP has comparable, or increased cancer survival relative to melanoma of known primary when stage is afforded for stage, which may be as a result of more vigorous immunologic activity. [9]

Melanoma is classified as a malignant melanocytic tumor within the WHO Classification of Skin Tumors (5th edition) based on molecular, histopathologic, and anatomic subtypes. [10] Metastatic melanoma is listed under this heading irrespective of primary site. [10] MUP is not a new, distinct histologic subtype but merely a clinical presentation of metastatic melanoma. Molecular features such as BRAF V600E mutations, as shown in this case, are common and have critical therapeutic implications, especially for targeted and immunotherapy-based treatments. [10,11]

3.2. Pathogenesis, Pathophysiology

Melanoma metastatic to distant organs from an unknown primary (MUP) is a type of melanoma that arises from the transformation of normal melanocytes within the body. Melanocytes are cells of neural crest origin that normally reside in the basal layer of the epidermis, as well as in the mucosal surfaces, the uveal tract of the eye, and in other ectopic locations within the body. The reason that a primary lesion of melanoma is not detectable in these individuals with MUP is not entirely understood. However, potential reasons for the lack of detectability of the primary tumor site for individuals with MUP may be that the tumor regressed spontaneously; that the body's immune system eliminated the cells that contained the melanoma; that the melanoma lesion was located in an area that was not detected, such as mucosal areas, or that the melanoma was excised from the body following its diagnosis as the body's primary tumor. [8]

Melanoma results from mutations in the genetic material of melanocytes that control their proliferation. Most melanomas have mutations that activate the MAPK (mitogen-activated protein kinase) pathway. In approximately 40–50% of individuals with melanoma, a mutation in the BRAF gene at V600E is present. This mutation activates the MAPK pathway, leading to uncontrolled melanocyte proliferation. Other mutations found in melanoma cells of those individuals that activate the MAPK pathway include mutations in NRAS and KIT. Additionally, melanoma cells typically harbor deletions of genes that normally regulate melanocyte growth, most notably CDKN2A. [12]

Melanoma cells are pleomorphic. Thus, the cells within a tumor containing melanoma may vary in their size, shape, and features. Additionally, those cells may contain intranuclear and cytoplasmic inclusions, as well as melanin pigment. Because melanin is present in those cells, the tumors can be stained with markers such as S100 protein, SOX10 protein, HMB-45, and Melan-A, all of which bind melanin. Because melanoma tumors lack markers of other cell types, these findings are further supportive of the melanocytic origin of the tumor. [4]

The growth and spread of melanoma can be explained, at least in part, by the interaction between tumor cells and the immune system. Additionally, it is often proposed that MUPs have a better prognosis than melanomas with a confirmed primary tumor. A better prognosis is often attributed to enhanced immune activity within the tumor microenvironment, which may have led to the original primary tumor disappearing, or "regressing". However, earlier studies have found that the two types of melanomas may have similar survival rates among individuals with melanoma after treatment. The consensus now strongly trends toward acknowledging a better prognosis, potentially due to distinct biology or immune-mediated control, making it a unique clinical entity [13,14]

Knowledge of the genetic alterations that lead to melanoma has led to targeted treatments for melanoma. For instance, drugs that target the BRAF V600E mutation inhibit the MAPK pathway, thereby minimizing melanocyte proliferation. Additionally, drugs such as anti-PD-1 and anti-CTLA-4 antibodies have improved survival rates in individuals with melanoma. [11,13,14]

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, lab, diagnosis, management, and outcome)

Our case aligns with the established epidemiological profile of MUP. The patient is a middle-aged man presenting with a painless, enlarging cervical lymph node, consistent with published data showing that cervical nodal involvement accounts for approximately 26–33% of MUP cases, and that the condition is more prevalent in men, typically in the fourth to fifth decade of life. [4,6]

The cytomorphologic findings on FNA mirror the morphologic spectrum described by Ronchi et al in their practical review of FNA cytology in metastatic melanoma, where these features were identified as hallmarks of the diagnosis. [15] The immunophenotype (S-100, SOX10, HMB-45, Melan-A positive; pan-cytokeratin, TTF-1, CD45, p63 negative) is precisely the panel recommended for confirmation and exclusion of competing diagnoses. [15]

Where our case diverges from many reported cases is in the completeness of the primary site exclusion workup. Scott et al., in a study of 103 MUP patients, found that subspecialty referrals rarely yielded a primary site, and some investigators have questioned their necessity. [6] Our patient, by contrast, underwent an exhaustive multidisciplinary evaluation, including dermoscopy, ophthalmologic examination, nasal endoscopy, cystoscopy, and proctoscopy, satisfying the stringent Das Gupta exclusion criteria, which are applied in only 16% of published MUP series. [6]

The BRAF V600E mutation, identified by NGS, is consistent with the 53% BRAF mutation prevalence reported by Gos et al. in 103 MUP patients with nodal metastases. [5] The management, selective neck dissection followed by adjuvant dabrafenib and trametinib, reflects the current standard of care, and the favorable outcome at 12 months is consistent with the improved survival reported by van der Ploeg et al. for stage III nodal MUP compared with MKP. [16]

4. 4. What Have We Learned from This Case?

We learn from this case that a painless, solitary cervical lymph node in a middle-aged man without constitutional symptoms is not a benign finding by default. Melanoma must sit high on the differential, even in the absence of an identifiable skin lesion, because the primary may have undergone immune-mediated regression before the patient noticed it. Recognition of a malignant melanocytic pattern on FNA smears, including dyscohesive, pleomorphic cells with intranuclear inclusions and pigment, can raise suspicion for melanoma and prompt immunohistochemical confirmation; if the lesion were instead interpreted as poorly differentiated carcinoma, diagnosis could be delayed, especially in amelanotic cervical melanoma. [17]

The cell block, prepared from residual FNA material, proved decisive: it enabled IHC and NGS on a single minimally invasive specimen, demonstrating that cytology alone, when thoughtfully processed, is sufficient to drive a complete oncologic diagnosis.

We learned that the absence of a known primary is not a diagnostic failure; it is a recognized entity with its own staging, biology, and prognosis. The thoroughness of the exclusion workup is what gives the MUP designation its integrity, and that thoroughness requires a coordinated multidisciplinary effort spanning dermatology, ophthalmology, ENT, and gastroenterology. The BRAF V600E mutation, identified in the cell block material, shifted management from a surgical-only approach to a combined-modality strategy, underscoring that molecular profiling of cytologic specimens should be routine rather than reflexive.

This case reinforces that FNA with cell block preparation and reflexive IHC and molecular testing should be the first-line approach to any unexplained cervical adenopathy in an adult.

Abbreviations: Melanoma of unknown primary (MUP); Melanoma of known primary (MKP). Fine-needle aspiration (FNA); Immunohistochemical (IHC).

5. Conclusion

This case illustrates that metastatic malignant melanoma of unknown primary is a diagnosis that demands both cytopathologic precision and clinical thoroughness. A 49-year-old man presenting with an isolated, painless posterior cervical node, unremarkable on surface examination, harbored a BRAF V600E-mutant melanoma confirmed entirely through ultrasound-guided FNA with cell block preparation, IHC, and next-generation sequencing, without a single surgical incision for diagnosis.

The case adds to the literature by demonstrating that this diagnostic triad, cytomorphology, immunophenotyping, and molecular analysis, is fully sufficient to establish an actionable oncologic diagnosis and guide multidisciplinary management, including targeted therapy. It also illustrates the clinical value of a rigorous, systematized exclusion workup in conferring the MUP designation with diagnostic confidence, rather than as a default label of exclusion. The patient's remission at twelve months, consistent with the relatively favorable prognosis of stage III nodal MUP reported in the literature, further supports treating this entity according to established guidelines for stage-matched melanoma of known primary.

Clinicians encountering unexplained cervical adenopathy should maintain a high index of suspicion for melanoma regardless of the absence of cutaneous findings, and pathologists should ensure that FNA specimens are optimally processed to enable the full complement of ancillary studies. Awareness of this entity and the diagnostic power of well-prepared cytology can prevent delays and open the door to timely, life-altering treatment.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

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- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of informed consent

The patient was lost to follow-up, and all attempts to reach the patient were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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