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## Capsular nevus versus metastatic malignant melanoma – a diagnostic dilemma

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## ABSTRACT

**INTRODUCTION:** A positive finding of metastatic melanoma in a sentinel lymph node is an ominous sign and a strong predictor of overall survival. In contrast, current data trends have shown that patients with benign nevus cells in the sentinel nodes do not require additional therapy since their prognosis has been shown to be similar to that of patients with negative lymph nodes. Distinguishing between benign capsular nevi and metastatic melanoma often proves to be diagnostically problematic.

**CASE PRESENTATION:** In this case report we present two cases of melanoma in which sentinel lymph node biopsies proved to be difficult in distinguishing metastatic melanocytes from capsular nevus cells. In both cases, further workup was necessary for accurate diagnoses.

**DISCUSSION:** A lack of standardized distinctions of benign nevus cell from melanoma pose a diagnostic pitfall. Assigning a diagnosis of malignant melanoma might seem like the safer approach to avoid a false negative, but the resultant treatment, including the possibility of additional surgical complications, may cause anxiety, discomfort, and financial instability for the patient. Current methods of distinguishing the two based solely on histology may be insufficient due to similar pathologic patterns.

**CONCLUSION:** To avoid misdiagnosing a patient and performing unnecessary therapy, it would be beneficial to get a second opinion by additional histopathologists at a high volume center. Additionally, immunohistochemical staining should be carefully employed due to some overlap in commonly used markers. Using tissue morphology in conjunction with immunohistochemical staining may be the best way to make the most accurate diagnosis.

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## 1. Background

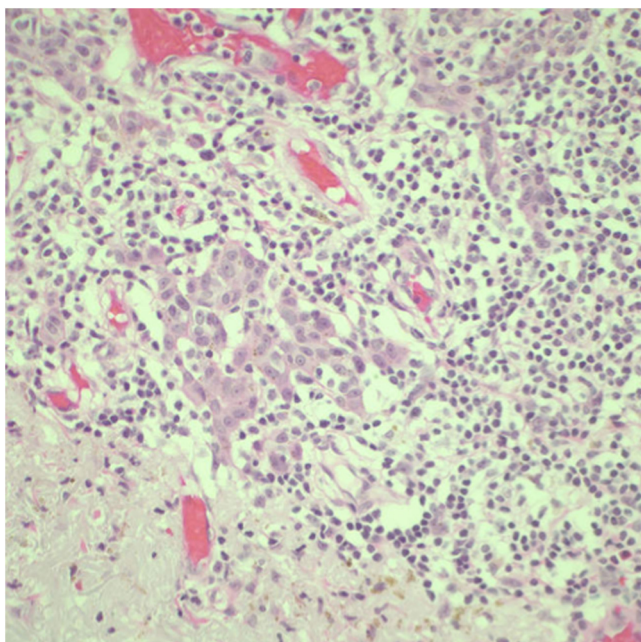
According to the American Joint Commission on Cancer (AJCC) standards, melanoma patients with specific primary lesions should undergo a sentinel lymph node biopsy for proper staging and diagnosis. AJCC guidelines for sentinel lymph node biopsy have been recently updated to include patients who have been staged as T1b primary lesions ( $\leq 1.0$  mm Breslow thickness with ulceration or mitoses  $\geq 1$  mm<sup>2</sup>) [1,2]. Thus, the increased use of sentinel lymph node biopsies in patients with melanoma have led to a higher frequency of nodal nevi discovered in regional lymph nodes [3,4]. Incidence of nodal aggregates of benign nevus cells in sentinel lymph node biopsies have shown to be as high as 22% in melanoma cases and often present in a confined fibrous capsule or trabeculae of lymph nodes [5,6].

A positive finding of metastatic melanoma in a sentinel lymph node is an ominous sign and a strong predictor of overall survival and progression [4]. In contrast, patients with benign nodal nevus aggregates have been shown to present with a 5 year survival similar to that of patients who had no positive findings on sentinel lymph node biopsies [7,8]. Thus, the differentiation between the nodal nevi and metastatic lymph nodes has a profound effect on the prognosis of the patient, as the recognition of the differences is important to avoid misdiagnosis and provide adequate therapy options [7–9]. Current gold standard for diagnosis of metastatic melanoma has been tissue morphology and histopathology; however, benign melanocytic nevus cells are often difficult to distinguish from metastatic melanoma [2,3,6,9,10].

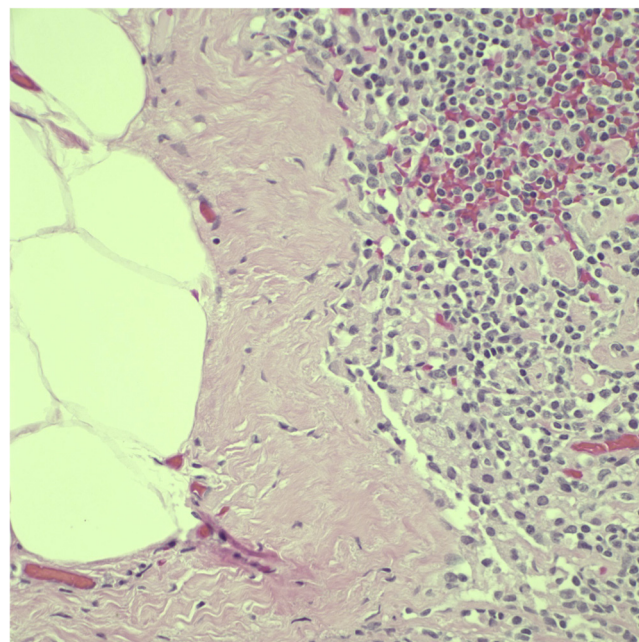
In this case report, which is in compliance with the CAse REport (SCARE) Guidelines, we present two cases of melanoma in which sentinel lymph node biopsies proved to be difficult in distinguishing metastatic melanocytes from capsular nevus cells [11]. In both cases, further workup was necessary for accurate diagnosis of disease status. We believe that advanced histopathological techniques should be employed in these scenarios given the significant

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**Fig. 1.** Case 1: H & E section of skin of left forearm after wide excision of melanoma 40x. Central area of organizing inflamed re-epithalized scar. The biopsy site at the edge where this is focal residual malignant melanoma invasive to a depth of 0.74 mm. The surrounding surface shows areas of residual radial growth phase/in situ melanoma.



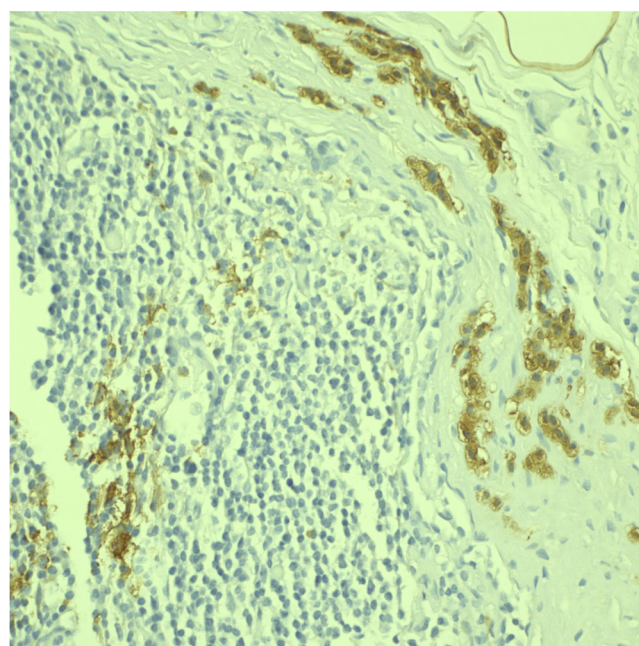
**Fig. 2.** Case 1: H & E view of the sentinel lymph node shows portions of capsule to be cauterized with central hilar fatty replacement. Sinus histiocytes are scattered in moderate numbers in the sinusoids. Indicative of capsular nevus.

differences in the possible diagnoses, as well as examination of tissue morphology. Additionally, we strongly encourage obtaining a second opinion of another histopathologist, preferably at a high volume center.

## 2. Case presentation

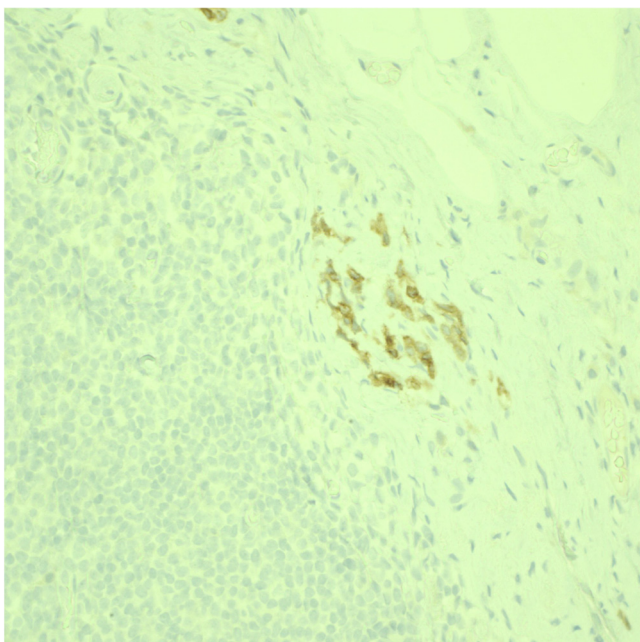
### 2.1. Case 1

- A 68-year-old male with a lesion on the posterior left forearm that presented one year ago and was initially treated with cryotherapy. Eight weeks prior, the patient noticed the lesion enlarging. Patient has a past medical history of atrial fibrillation treated with anticoagulant therapy as well as squamous cell carcinoma of the skin. Patient has a past surgical history of pacemaker placement, heart valve replacement, splenectomy, and nasal septal deviation repair. He has family history of a cardiac disorder and colon cancer. Patient denies smoking.
- A shave biopsy of 2 cm × 2 cm on the left forearm identified superficial spreading melanoma of 2.1 mm thickness, high mitotic index, and ulceration with positive margins that was staged as T3a. A wide local excision with 2 cm margins and sentinel lymph node biopsy due to positive margins & intermediate thickness was performed. The tumor size was 1.21 cm with a maximum thickness at 2.3 mm and staged at pT3aN0M0. Pathology of the re-excisional biopsy showed focal residual malignant melanoma invasive to 0.74 mm with atypia and overlying epidermis with residual in situ melanoma (Fig. 1). Peripheral and deep margins were uninvolved. No lymphovascular invasion or microsatellitosis was identified. 2 non-sentinel lymph nodes were examined and showed no regional lymph node metastasis. 1 sentinel lymph node showed 0.4 mm focus within nodal capsule with positive S100 and MART-1 staining that was suspicious for capsular nevus vs. less likely metastases due to lack of cellular atypia and other morphological signs. These slides were sent to an outside institution for second opinion. The reports identified, first, the primary

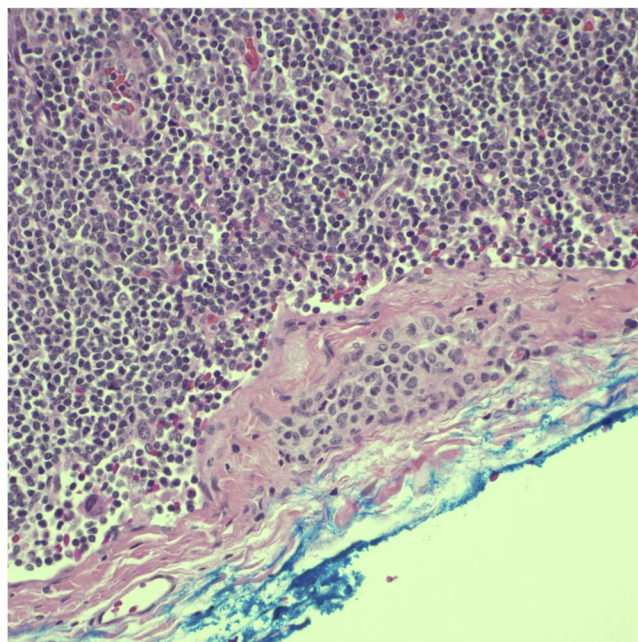


**Fig. 3.** Case 1: S-100 immunostain shows 0.4 mm focus of small bland appearing cells within the capsule of sentinel lymph node that are not discretely identifiable on H & E stained section levels but appear to have small round nuclei.

tumor to be a residual melanoma invasive to 0.74 mm, classified as lentigo maligna melanoma. Morphological observations of sentinel lymph nodes were consistent with capsular nevus (Fig. 2). Sentinel lymph node was positive for Melan-A, S100 (Fig. 3), and MART-1 (Fig. 4). However, it was negative for HMB-45, which helped confirm a benign diagnosis. The second opinion agreed that the sentinel node was more consistent with capsular nevus rather than malignant melanoma.



**Fig. 4.** Case 1: MART-1 immunostain shows 0.4 mm focus of small bland appearing cells within the capsule that are not discretely identifiable on H & E stained section levels but appear to have small round nuclei.



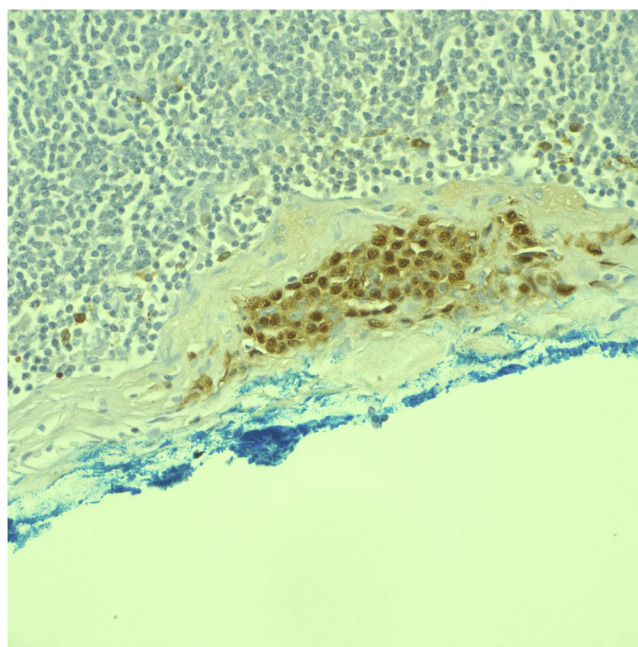
**Fig. 5.** Case 2: H & E of sentinel lymph node shows bland melanocytes within the capsule with uncertain significance.

## 2.2. Case 2

- A 57-year-old male with a gradually enlarging lesion on the right flank. Patient denied any pain or associated symptoms with the lesion. Patient has a past medical history of hypertension, past surgical history of knee surgery, and family history of cardiac disorders. Patient denies smoking, alcohol, or illicit drug use. There were no palpable cervical, supraclavicular or axillary nodes on physical exam.
- A shave biopsy of 2 cm × 1.5 cm identified superficial spreading melanoma of 1.01 mm thickness with <1 mm<sup>2</sup> mitotic index, and non-ulcerated. Deep and lateral margins were positive and the tumor was clinically staged at T2a. A wide local excision with 2 cm margins and sentinel lymph node biopsy was performed due to intermediate thickness melanoma. The wide local excision pathologically demonstrated no residual malignant melanoma, no lymphovascular invasion, or microsateliosis. The peripheral and deep margins were uninvolved. Four non-sentinel lymph nodes all showed no metastatic melanoma; three were S-100 negative, and all four were SOX10 and MART-1 negative. One sentinel node demonstrated bland melanocytes within the capsule of uncertain significance and could represent benign nevus cells but identification was not certain (Fig. 5). A consultative review was sent to an outside institution. These reports stated that the excisional biopsy demonstrated no residual melanoma and the sentinel node showed aggregates of melanocytic cells present within the capsule. These aggregates were of a lesser degree of atypia compared to primary tumor but were S100 (Fig. 6) and MART-1 (Fig. 7) positive. They concluded that the cells were more likely capsular nevus vs. metastatic melanoma.

## 3. Discussion

Benign nevus cell aggregates within lymph nodes is a well-described finding; however, there are no standardized ways to distinguish them from metastatic melanocytes and thus pose a diagnostic pitfall to pathologists. While there are many morphologic guidelines to recognize nodal nevus cells, there are some



**Fig. 6.** Case 2: S100 immunostain of sentinel lymph node capsule showed to be positive.

cases where the diagnosis may not be as straightforward and the prediction of behavior of certain cells may not be accurate solely based on histopathological findings [9]. Current data trends have definitively indicated that patients with benign nevus aggregates in the sentinel nodes do not require additional lymphadenectomies and pharmacologic therapies as their prognosis is similar to that of patients with negative sentinel lymph nodes [8]. Assigning a diagnosis of malignancy might seem like the safer approach, but it can result in excessive treatment, which leads to the possibility of surgical complications, anxiety, discomfort, and financial instability for the patient. Thus, a careful diagnostic approach should be taken in patients with questionable sentinel lymph nodes to con-

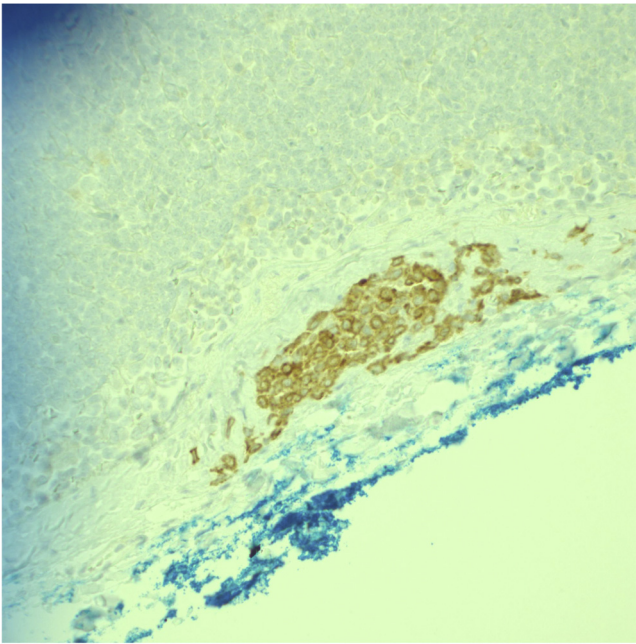


Fig. 7. Case 2: MART-1 immunostain for sentinel lymph node shown to be positive.

firm any metastatic disease before starting aggressive therapy to treat metastatic melanoma. Current methods of distinguishing the two based solely on histology may be insufficient due to the similar pathologic patterns between melanoma and capsular nevi cells.

The exact mechanism by which nevus cells arrive to the lymph nodes has not been established, but the mechanical transport theory has been the most favored amongst most studies [3,4,7,9]. This theory proposes that a neoplastic melanocyte displaces the adjacent nevus cells, which are then transported into the lymphatics. It is then assumed that the benign nevi hone to the fibrous tissue of the capsule, trabeculae, or even sometimes node parenchyma, which may explain the high prevalence in regional sentinel lymph nodes [5]. Nevus cells have a particular morphology and lack the identifying characteristics associated with melanoma, including large cells, numerous mitotic figures, large nuclear to cytoplasm ratio, and pleomorphism [12].

Immunohistochemistry studies can play a helpful role, but are not definitive in distinguishing nodal nevus from melanoma. Nodal nevi have shown to be positive for S-100 and MART-1 stains, which are both thought to be highly sensitive markers for metastatic melanocytes. Thus, these are inconclusive markers for correctly distinguishing benign from malignant cells [5,6]. Additional studies have shown that nevus cells are often absent or only focally positive for HMB-45 (gp-100) while most metastatic melanoma often stain strongly for HMB-45. However, not all metastatic melanomas are positive for HMB-45, thus an absence does not rule out the diagnosis of melanoma [5,13]. Studies have also demonstrated that Ki-67 immunohistochemical (IHC) markers are positive in less than 1% of benign nevus cells and the lack of Ki-67 may further confirm the presence of benign nevus aggregates [5,6]. Furthermore, the presence of SOX10 protein, as well as MART-1, is strong predictor of malignant melanoma [14,15]. Many recent studies advocate the use of these IHC markers to help confirm suspicious lymph node biopsies. However, no one marker has shown to be diagnostic at this time and no one study has identified which ones should be standard markers in ambiguous biopsy findings.

#### 4. Conclusion

These two cases presented a diagnostic dilemma and allow for discussion regarding the best approach in similar patients where an absolute diagnosis is difficult. IHC staining should be employed carefully in making a distinction between benign and metastatic cells due to some overlap in commonly used markers. The best way to assign the most accurate diagnosis to the sentinel lymph node biopsy is to compare both the morphology and staining characteristics between the primary melanoma lesion and the lymph node, as well as using as many different staining methods as possible. Additionally, in order to avoid misdiagnosing a patient and performing unnecessary further therapy, it would be beneficial to get a second opinion by another histopathologist at a high volume center.

#### Conflicts of interest

The authors of this paper report no conflicts of interest.

#### Funding

There was no funding necessary for this research.

#### Ethical approval

There was no required ethical approval for this study.

#### Author contribution

Justin Davis – Primary author  
 Dr. Patil – Secondary author  
 Dr. Aydin – Critical revisions  
 Dr. Mishra – Critical revisions  
 Dr. Misra – Concept

#### Disclosure statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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