Diagnostic Value of Deep Punch Biopsies in Intravascular Large B-cell Lymphoma

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PRACTICE **POINTS**

- Skin biopsy is an effective method for identifying intravascular large B-cell lymphoma (IVBCL).
- Deep punch biopsies of sites involving hemangiomas may further heighten sensitivity for detection of IVBCL, as these lesions may harbor increased numbers of intravascular lymphoma cells.
- Deep and strategically placed skin biopsies offer potential improvements in timely diagnosis and outcomes of patients with IVBCL.

The purpose of this study was to determine the diagnostic efficacy of skin biopsies for detecting intravascular large B-cell lymphoma (IVBCL) at various body sites and to establish whether biopsies from hemangiomas yield higher diagnostic value. Postmortem 4-mm punch biopsies were collected from various anatomic sites of a patient with IVBCL, including random areas of the skin as well as targeted areas (hemangiomas). Each biopsy was evaluated to assess the degree and depth of IVBCL involvement. The primary study outcome measurement was the presence and extent of IVBCL involvement in skin biopsies. Involvement was graded on a scoring system that assessed IVBCL in vascular lumina and depth in the skin. Skin biopsy is a sensitive, cost-efficient method for IVBCL assessment, and optimizing biopsy strategies will improve diagnostic accuracy and subsequently patient outcomes.

Intravascular large B-cell lymphoma (IVBCL) is an exceedingly rare aggressive form of non-Hodgkin lymphoma with tumor cells growing selectively in vascular lumina.[1] The annual incidence of IVBCL is fewer than 0.5 cases per 1,000,000 individuals worldwide.[2] Only about 500 known cases of IVBCL have been recorded in the literature,[3] and it accounts for less than 1% of all lymphomas. It generally affects middle-aged to elderly individuals, with an average age at diagnosis of 70 years.[2] It has a predilection for men and commonly develops in individuals who are immunosuppressed.[3,4]

Multiple variants of IVBCL have been described in the literature, with central nervous system and cutaneous involvement being the most classic findings.[5] Bone marrow involvement with hepatosplenomegaly also has been noted in the literature.[6,7] Diagnosis of IVBCL and its variants requires a high index of suspicion, as the clinical manifestations and tissues involved typically are nonspecific and highly variable. Even in the classic variant of IVBCL, skin involvement is only reported in approximately half of cases.[3] When present, cutaneous manifestations can range from nodules and violaceous plaques to induration and telangiectasias.[3] Lymphadenopathy and lymphoma (leukemic) cells are not seen on a peripheral blood smear.[2,8,9]

The lack of lymphadenopathy or identifiable leukemic cells in the peripheral blood presents a diagnostic dilemma, as sufficient information for accurate diagnosis must be obtained while minimizing invasive procedures and resource expenditure. Because IVBCL cells can reside in the vascular lumina of various organs, numerous biopsy sites have been proposed for diagnosis of lymphoma, including the bone marrow, skin, prostate, adrenal gland, brain, liver, and kidneys.[10] While some studies have reported that the optimal diagnostic site is the bone marrow, skin biopsies are more routinely carried out, as they represent

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The eTable and eFigures are available in the Appendix online at www.mdedge.com/cutis.

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a convenient and cost-effective alternative to other more invasive techniques.[6,7,10] Studies have shown biopsy sensitivity values ranging from 77.8% to 83.3% for detection of IVBCL in normal-appearing skin, which is comparable to the sensitivities of a bone marrow biopsy.[7,8] Although skin biopsy of random sites has shown diagnostic efficacy, some studies have proposed that biopsies taken from hemangiomas and other hypervascular lesions can further improve diagnostic yield, as lymphoma cells often are present in capillaries of subcutaneous adipose tissue.[6,10,11] However, no obvious clinicopathologic differences were observed between IVBCL with and without involvement of a cutaneous hemangioma.[11]

The purpose of this study was to determine the diagnostic efficacy of skin biopsies for detecting IVBCL at various body sites and to establish whether biopsies from hemangiomas yield higher diagnostic value.

Methods

A 66-year-old man recently died at our institution secondary to IVBCL. His disease course was characterized by multiple hospital admissions in a 6-month period for fever of unknown origin and tachycardia unresponsive to broad-spectrum antibiotics and systemic steroids. The patient declined over the course of 3 to 4 weeks with findings suggestive of lymphoma and tumor lysis syndrome, and he eventually developed shock, hypoxic respiratory failure, and acute renal failure. As imaging studies and examinations had not shown lymphadenopathy, bone marrow biopsy was performed, and dermatology was consulted to perform skin biopsies to evaluate for IVBCL. Both bone marrow biopsies and random skin biopsies from the abdomen showed large and atypical CD20+ B cells within select vascular lumina (Figure 1). No extravascular lymphoma cells were seen. Based on the bone marrow and skin biopsies, a diagnosis of IVBCL was made. Unfortunately, no progress was made clinically, and the patient was transitioned to comfort measures. Upon the patient's death, his family expressed interest in participating in IVBCL research and agreed to a limited autopsy consisting of numerous skin biopsies to evaluate different body sites and biopsy types (normal skin vs hemangiomas) to ascertain whether diagnostic yield could be increased by performing selective biopsies of hemangiomas if IVBCL was suspected.

Twenty-four postmortem 4-mm punch biopsies containing subcutaneous adipose tissue were taken within 24 hours of the death of the patient before embalming. The biopsies were taken from all regions of the body except the head and neck for cosmetic preservation of the decedent. Eighteen of the biopsies were taken from random sites of normal-appearing skin; the remaining 6 were taken from clinically identifiable cherry hemangiomas (5 on the trunk and 1 on the thigh). There was a variable degree of livor mortis in the dependent areas of the body, which was included in the random biopsies from the back to ensure any pooling of dependent blood would not alter the findings.

A histopathologic examination by a board-certified dermatopathologist (M.P.) on a single hematoxylin-eosin–stained level was performed to evaluate each biopsy for superficial involvement and deep involvement by IVBCL. Superficial involvement was defined as dermal involvement at or above the level of the eccrine sweat glands; deep involvement was defined as dermal involvement beneath the eccrine sweat glands and all subcutaneous fat present. Skin and bone marrow biopsies used to make the original diagnosis prior to the patient's death were reviewed, including CD20 immunohistochemistry for morphologic comparison to the study slides. Involvement was graded as 0 to 3+ (eTable).

Results

Results from all 24 biopsies are shown in the eTable. Twenty-two (91.7%) biopsies showed at least focal involvement by IVBCL. Nine (37.5%) biopsies showed more deep vs superficial involvement of the same site. On average, the 6 biopsies from clinically detected

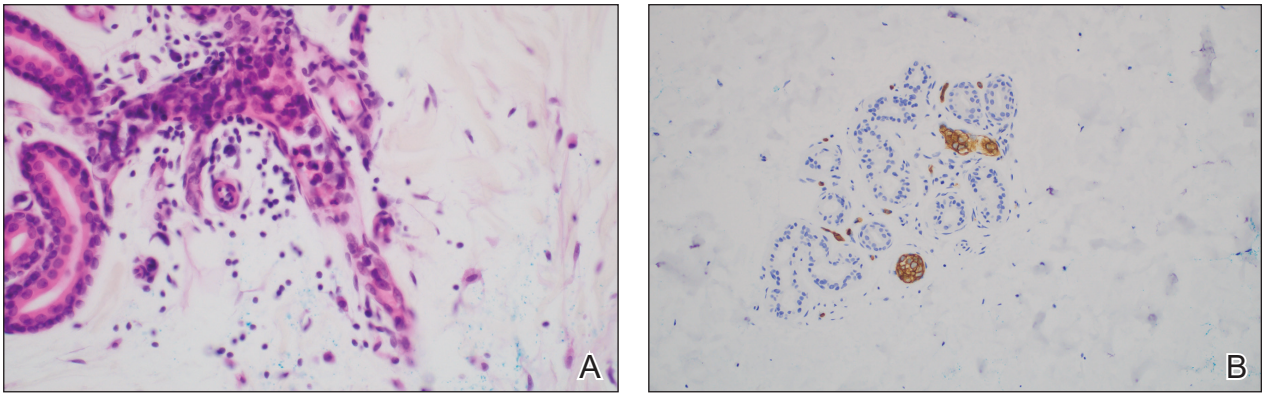

FIGURE 1. A, A high-power image from the original biopsy of the patient prior to death showed large atypical mononuclear cells within deep capillaries adjacent to the eccrine ducts (H&E, original magnification ×400). B, CD20 immunohistochemistry confirmed the large mononuclear cells were B cells (original magnification ×200).

hemangiomas showed more involvement by IVBCL than the random biopsies (eFigures 2 and 3A). The superficial involvement of skin with a hemangioma showed an average score of 2.33 v 0.78 when compared with the superficial aspect of the random biopsies; the deep involvement of skin with a hemangioma showed an average score of 2.67 vs 1.16 when compared with the deep aspect of the random biopsies (eFigure 3B).

Comment

Intravascular large B-cell lymphoma is an aggressive malignancy that traditionally is difficult to diagnose. Many efforts have been made to improve detection and early diagnosis. As cutaneous involvement is common and sometimes the only sign of disease, dermatologists may be called upon to evaluate and biopsy patients with this suspected diagnosis. The purpose of our study was to improve diagnostic efficacy by methodically performing numerous biopsies and assessing the level of involvement of the superficial and deep skin as well as involvement of hemangiomas. The goal of this meticulous approach was to identify the highest-yield areas for biopsy with minimal impact on the patient. Our results showed that random skin biopsies are an effective way to identify IVBCL. Twenty-two (91.7%) biopsies contained at least focal lymphoma cells. Although the 2 biopsies that showed no tumor cells at all happened to both be from the left arm, this is believed to be coincidental. No discernable pattern was identified regarding involvement and anatomic region. Even though 20 (83.3%) biopsies showed superficial involvement, deep biopsy is essential, as 9 (37.5%) biopsies showed increased deep involvement compared to superficial involvement. Therefore, a deep punch biopsy is essential for maximum sensitivity.

Hemangiomas provide a potential target that could increase the sensitivity of a biopsy in the absence of clinical findings, when the disease in question is exclusively intravascular. The data gathered in this study support this idea, as biopsies from hemangiomas showed increased involvement compared to random biopsies, both superficially and deep (2.33 vs 0.78 and 2.67 vs 1.16, respectively). Interestingly, the hemangioma biopsy sites showed increased deep and superficial involvement, despite these typical cherry hemangiomas only involving the superficial dermis. One possible explanation for this is that the hemangiomas have larger-caliber feeder vessels with increased blood flow beneath them. It would then follow that this increased vasculature would increase the chances of identifying intravascular lymphoma cells. This finding further accentuates the need for a deep punch biopsy containing subcutaneous fat.

Completing the study in the setting of an autopsy provided the advantage of being able to take numerous biopsies without increased harm to the patient. This extensive set of biopsies would not be reasonable to complete on a living patient. This study also has limitations. Although this patient did fall within the typical demographics for patients with IVBCL, the data were still limited to 1 patient. This autopsy format (on a patient whose cause of death was indeed IVBCL) also implies terminal disease, which may mean the patient had a larger disease burden than a living patient who would typically be biopsied. Although this increased disease burden may have increased the sensitivity of finding IVBCL in the biopsies of this study, this further emphasizes the importance of trying to determine any factors that could increase sensitivity in a living patient with a lower disease burden.

Conclusion

Skin biopsies can provide a sensitive, low-cost, and low-morbidity method to assess a patient for IVBCL. Though random skin biopsies can yield valuable information, deep, 4-mm punch biopsies of clinically identifiable hemangiomas may provide the highest sensitivity for IVBCL.

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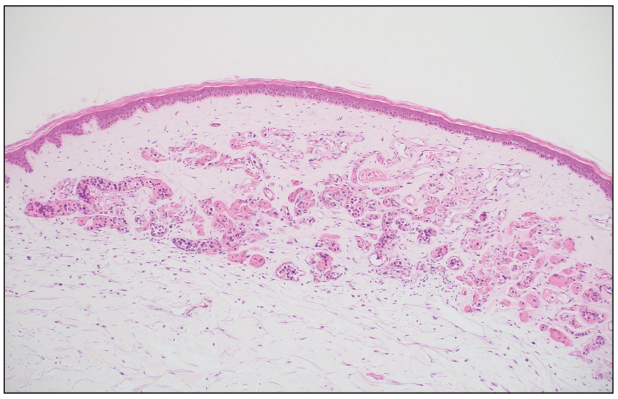
APPENDIX

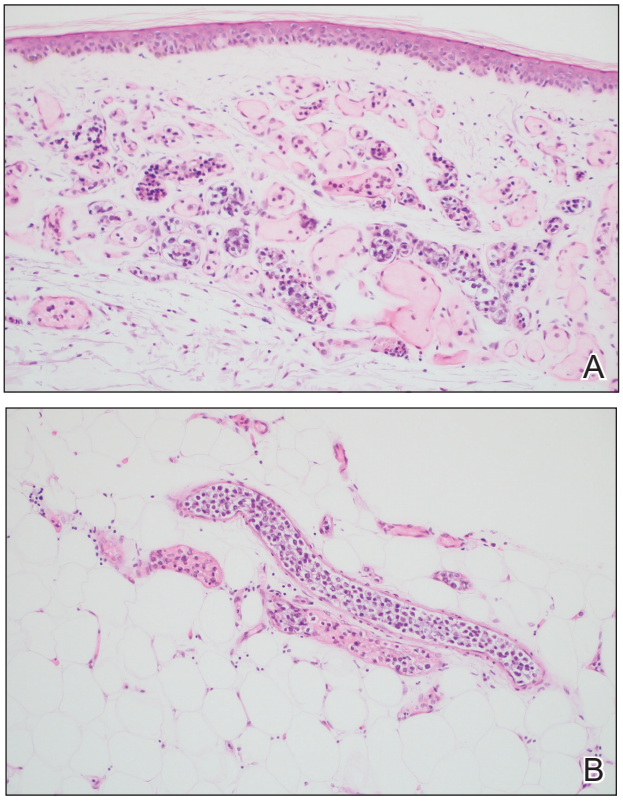
eTABLE. Study Biopsy Results

Site	Superficial involvement[a]	Deep involvement[a]
Left abdomen adjacent to diagnostic biopsy	1+	2+
	1+	1+
Abdominal fat pad	1+	1+
	1+	2+
Right chest	1+	1+
Left chest	0	1+
Right upper arm	1+	1+
Right lower arm	1+	1+
Left upper arm	0	0
Left lower arm	0	0
Right thigh	1+	2+
Right lower leg	1+	1+
Left thigh	1+	2+
Left lower leg	0+	1+
Left upper thigh hemangioma	3+	3+
Abdominal hemangioma	2+	3+
Right chest hemangioma	1+	3+
Right flank hemangioma	3+	3+
Right upper back	1+	1+
Right lower back	1+	1+
Left flank hemangioma	3+	2+
Left upper back	1+	1+
Left lower back	1+	2+
Left lower back hemangioma	2+	2+

[a]0 indicates no involvement; 1+ indicates rare focal tumor cells (<10% of vessels); 2+ indicates tumor cells easily identifiable in <50% of vessels; 3+ indicates tumor cells easily identifiable in ≥50% vessels.



eFIGURE 2. Superficial aspect of a punch biopsy of a clinical hemangioma demonstrated substantial involvement with prominent large, atypical lymphocytes filling more than half of the vessels (H&E, original magnification ×100).



eFIGURE 3. A, Another hemangioma demonstrated substantial involvement with atypical lymphocytes (H&E, original magnification ×200). B, Deep aspect of the punch biopsy demonstrated vessels within the subcutaneous fat that were dilated and filled with large atypical lymphocytes (H&E, original magnification ×200).