



RESEARCH ARTICLE

Sonographic features of secondary involvement of skin and subcutaneous tissues by hematologic malignancies

Heng Lyu MD¹  | Xiang Mei Chen MD¹ | Guang Yin Yu MD² |
Hong Jin Wang MD³ | De Sheng Sun MD¹  | Yu Shi MD¹ | Hai Qin Xie MD¹

¹Department of Ultrasound, Peking University Shenzhen Hospital, Shenzhen, China

²Department of Pathology, Peking University Shenzhen Hospital, Shenzhen, China

³Shenzhen Mindray Bio-medical Electronics Co. Ltd, Shenzhen, China

Correspondence

Hai Qin Xie, Department of Ultrasound, Peking University Shenzhen Hospital, 1120 Lianhua Road, Futian District, Shenzhen 518000, China.

Email: xiehaiqin@126.com

Funding information

The Science Technology and Innovation Commission of Shenzhen Municipality in China, Grant/Award Number: JCYJ20210324110015040; The Shenzhen Key Medical Discipline Construction Fund, Grant/Award Number: SZXK051; The Guangdong High-level Hospital Construction Fund, Grant/Award Number: GD2019260; The Shenzhen Virtual Reality Clinical Application Public Service Platform Promotion Project, Grant/Award Number: XMHT20190104001

Abstract

Objectives: To evaluate the sonographic features of secondary involvement of skin and subcutaneous tissues by hematologic malignancies.

Methods: A review of the ultrasound and pathology databases yielded 10 cases with 13 skin and subcutaneous tissue lesions secondary to hematologic neoplasms, which were confirmed by pathology. We used ultrasound to assess the number, location, size, depth of involvement, echogenicity, and vascularity of the lesions.

Results: The study involved five male and five female patients, including four leukemia, two multiple myeloma, and four lymphoma patients. The average age was 45 years (17–66 years). Three patients presented with one lesion, four with two lesions, and three with more than two lesions. All the lesions were located in the trunk and extremities. The lesions ranged from 1.2 to 8.3 cm in size. A total of 10 lesions involved subcutaneous fat tissue. A total of 10 lesions displayed hypoechoic foci within a hyperechoic background, and three appeared hypoechoic, and most of them exhibited abundant vascularity (12 of 13 lesions).

Conclusions: Secondary involvement of skin and subcutaneous tissues by hematologic malignancies often present with multiple palpable masses showing the following ultrasound features: (1) subcutaneous fat infiltration, (2) hypoechoic foci with a hyperechoic background, and (3) abundant vascularity.

KEYWORDS

hematologic neoplasms, soft tissue, ultrasound

1 | INTRODUCTION

Hematologic neoplasms are tumors in the blood and blood-forming tissue (the bone marrow and lymphatic tissue), including leukemia, lymphoma, and multiple myeloma, accounting for about 9% of all neoplasms.¹ Hematologic neoplasms can involve the skin as a site of secondary involvement. Cutaneous manifestations of hematologic

neoplasms can be divided into specific and non-specific.² Specific cutaneous manifestations, infiltrated with malignant hematopoietic cells in the skin, and subcutis, are detected in 15.1% of cases.³ Non-specific cutaneous manifestations include paraneoplastic syndromes, drug reactions, opportunistic infections, and other conditions related to myelosuppression. Specific cutaneous infiltration in patients with hematologic neoplasms suggests a poor prognosis.³ The reported

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Journal of Clinical Ultrasound* published by Wiley Periodicals LLC.

TABLE 1 Demographic data and sonographic findings for all patients

No.	Sex	Age (year)	Primary tumor	Time to skin involvement after diagnosis (month)	Overall survival since skin involvement (month)	Cutaneous manifestations	Number of Lesions	location in the body	Size (mm)	Depth of involvement ^a	Echogenicity ^b	Vascularity
1	M	42	IgG MM	84	12	Nodular	2	Abdominal wall	83	(3)	(1)	Abundant
2	M	66	IgD MM	29	8	Nodular	2	Lower back	20	(2)	(1)	Abundant
3	F	43	AML	0	10	Papule, plaque, nodular	1	Lower back	22	(2)	(1)	Abundant
4	F	27	ALL	18	15	Nodular	2	Left thigh	17	(1)	(2)	Abundant
5	M	65	AML	16	12	Papule, plaque, nodular	1	Right thigh	22	(1)	(2)	Abundant
6	M	41	AML	3	15	Nodular	Numerous	Left forearm	65	(1) + (2)	(1)	Abundant
7	F	66	T-NHL	12	10	Nodular	Numerous	Right thigh	12	(2)	(1)	Abundant
8	M	38	B-NHL	48	16	Nodular	Numerous	Right upper arm	52	(2)	(1)	Abundant
9	F	17	T-NHL	24	22	Nodular	1	Chest wall	17	(1) + (2)	(1)	Minimal
10	F	45	B-NHL	15	36	Nodular	2	Abdominal wall	30	(1) + (2)	(2)	Abundant
						Nodular	2	Left foot	20	(1) + (2)	(1)	Abundant

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-NHL, B-cell non-Hodgkin lymphomas; F, female; IgD MM, immunoglobulin D multiple myeloma; IgG MM, immunoglobulin G multiple myeloma; M, male; T-NHL, T-cell non-Hodgkin lymphomas.

^a(1) Skin involvement; (2) Subcutaneous fat involvement; (3) Muscle involvement.

^b(1) Hypoechoic foci within a hyperechoic background; (2) Hypoechoic.

median survival time for patients with cutaneous involvement varied from 4.5 to 12.0 months among the published series.⁴⁻⁶ The mortality rate in patients with specific cutaneous manifestations was 18.2%, compared to 4.1% in patients without these lesions.³ Therefore, specific cutaneous manifestations are crucial indications in determining disease staging and prognosis.

The diagnosis of cutaneous involvement is mainly based on skin morphology and confirmed by skin biopsy.⁷⁻⁸ Nodules, plaques, papulo-nodular, and papules are four predominant morphologies of specific cutaneous manifestations found in patients with hematologic neoplasms.⁷ The infiltrated locations may include epidermis, dermis, or hypodermis. In previous works of literature, studies of specific cutaneous infiltration of hematologic neoplasms were primarily focused on skin morphology. A few papers described skin and subcutaneous tissue imaging characteristics involved in hematologic neoplasms. In the study by Lee et al., CT and MRI findings of superficial soft tissue lymphomas were non-specific.⁹ To our knowledge, no systematic review has been done for ultrasound findings of skin and subcutaneous tissue involvement in hematologic neoplasms. With high accessibility and excellent spatial resolution, ultrasound has become an ideal modality for examining skin, and subcutaneous tissue.¹⁰

We, therefore, sought to describe and systematically analyze the ultrasound findings of 10 patients with skin and subcutaneous tissue involvement in hematologic neoplasms.

2 | PATIENTS AND METHODS

2.1 | Patients

Our hospital institutional review board approved this retrospective study, waiving informed consent. We reviewed ultrasound and pathology databases to diagnose patients with hematologic neoplasms. We analyzed the ultrasound findings of 10 patients diagnosed with secondary cutaneous involvement of systemic hematologic neoplasms between January 2017 and July 2021. All patients underwent ultrasound examination, because of superficial palpable masses or infiltrated skin lesions, before needle biopsy or surgical resection. A total of 13 lesions were confirmed as skin and subcutaneous tissue involvement by pathology. The lesions were biopsied or surgically removed 1-11 days after ultrasound examination (mean 3 days). Clinical data were obtained by reviewing electronic medical records and from follow-up information provided

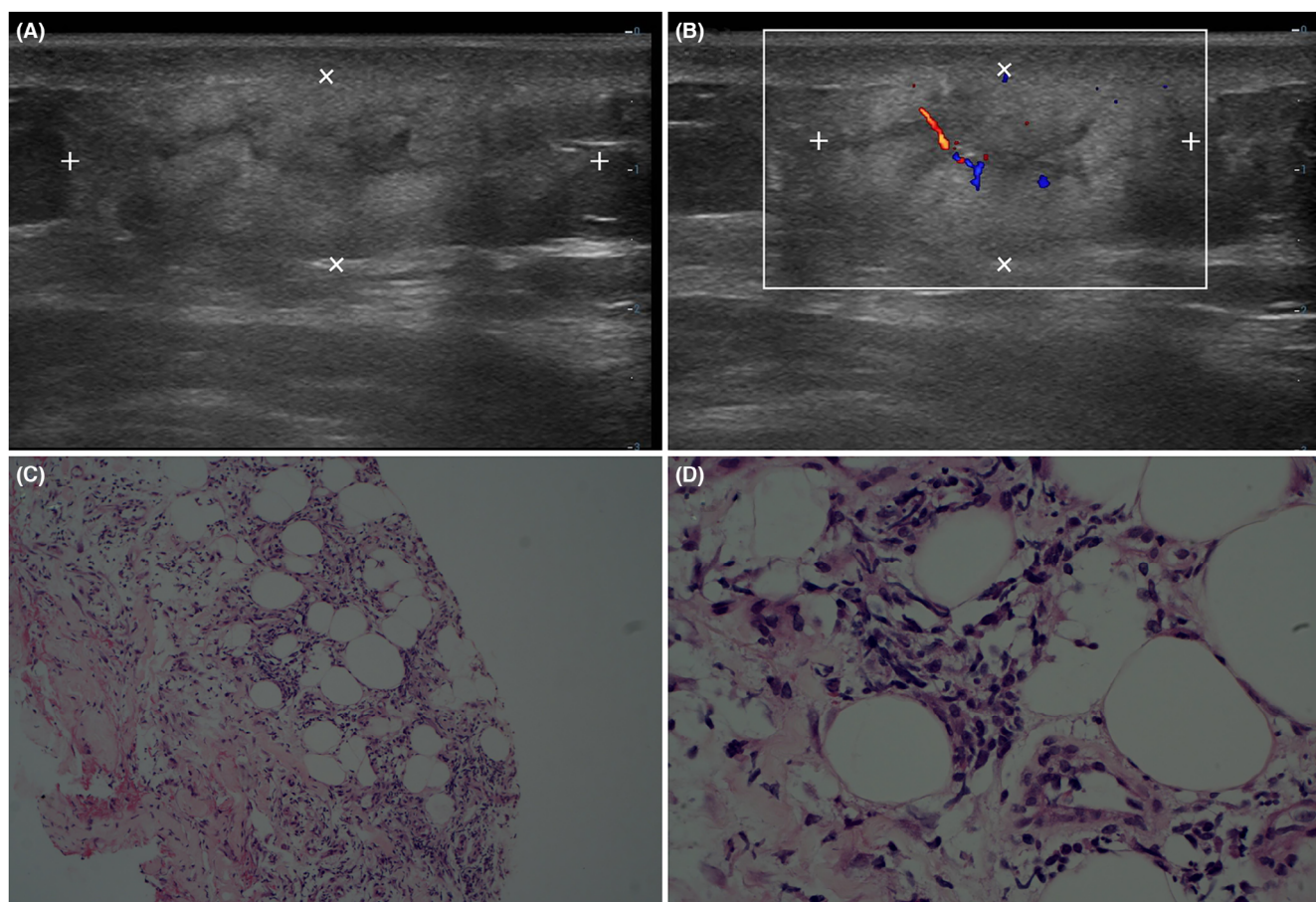


FIGURE 1 Leukemia involving the lower back in a 43-year-old woman (case 3): (A) Sonogram shows hypoechoic foci within a hyperechoic background on the lower back. (B) Color Doppler sonogram shows abundant vascularity. (C, D) Biopsy specimen (hematoxylin-eosin, original magnification 100, 400) of areas dominated by hyperechoic echogenicity shows that lymphoid cells cluster in a background of adipocytes.

by the patients' physicians. The clinical data included types of primary tumor, time for skin involvement after diagnosis, survival time after skin involvement, and cutaneous manifestations.

2.2 | Sonographic examinations and image analysis

Two musculoskeletal sonologists with over 5 years of experience analyzed the ultrasound images. Ultrasound systems used for the study were as follows: SuperSonic Aixplorer ultrasound system (SuperSonic Imagine) with a 15–4 MHz high-frequency linear array; Mindray Resona7 ultrasound system (Mindray) with a 14–5 MHz high-frequency linear array; Aplio 500 ultrasound system (Toshiba Medical Systems) with a 14–5 MHz high-frequency linear array. Two sonologists reviewed all available ultrasound images and decided on all interpretations based on consensus. If not, a third sonologist was involved.

The following sonographic features of skin and subcutaneous tissue involvement in hematologic neoplasms were evaluated: (1) Number of lesions; (2) Location in the body; (3) Size, including peripheral hyperechoic region of the lesion, measured using the longest diameter in the largest plane. (4) Depth of involvement as follows: (i) skin (dermis and

epidermis), (ii) subcutaneous fat, and (iii) muscle involvement. If the lesion involved both skin and subcutaneous fat, it was labeled as (i) + (ii). (5) Echogenicity, evaluated comparing the lesion with the echogenicity of adjacent tissue. (6) Vascularity. The vascularity of the lesions on color Doppler sonography was assessed according to Adler grade classifications and classified into four levels.¹¹ Grade 0–1 indicated low vascularity, while grade 2–3 indicated high vascularity. The color scale was adjusted to 3–8 cm/sec, and the color Doppler gain was set just below the color noise threshold to visualize the low-velocity flow.

3 | RESULTS

3.1 | Clinical findings

Patients' demographic information and clinical features were shown in Table 1. The average age of the 10 patients was 45 years (range, 17–66 years), including four leukemia, two multiple myeloma and four lymphoma patients. Nine patients developed skin and subcutaneous tissue lesions within 3–84 months after the onset of hematologic neoplasms, and one patient started simultaneously (mean time 24.9 months). The

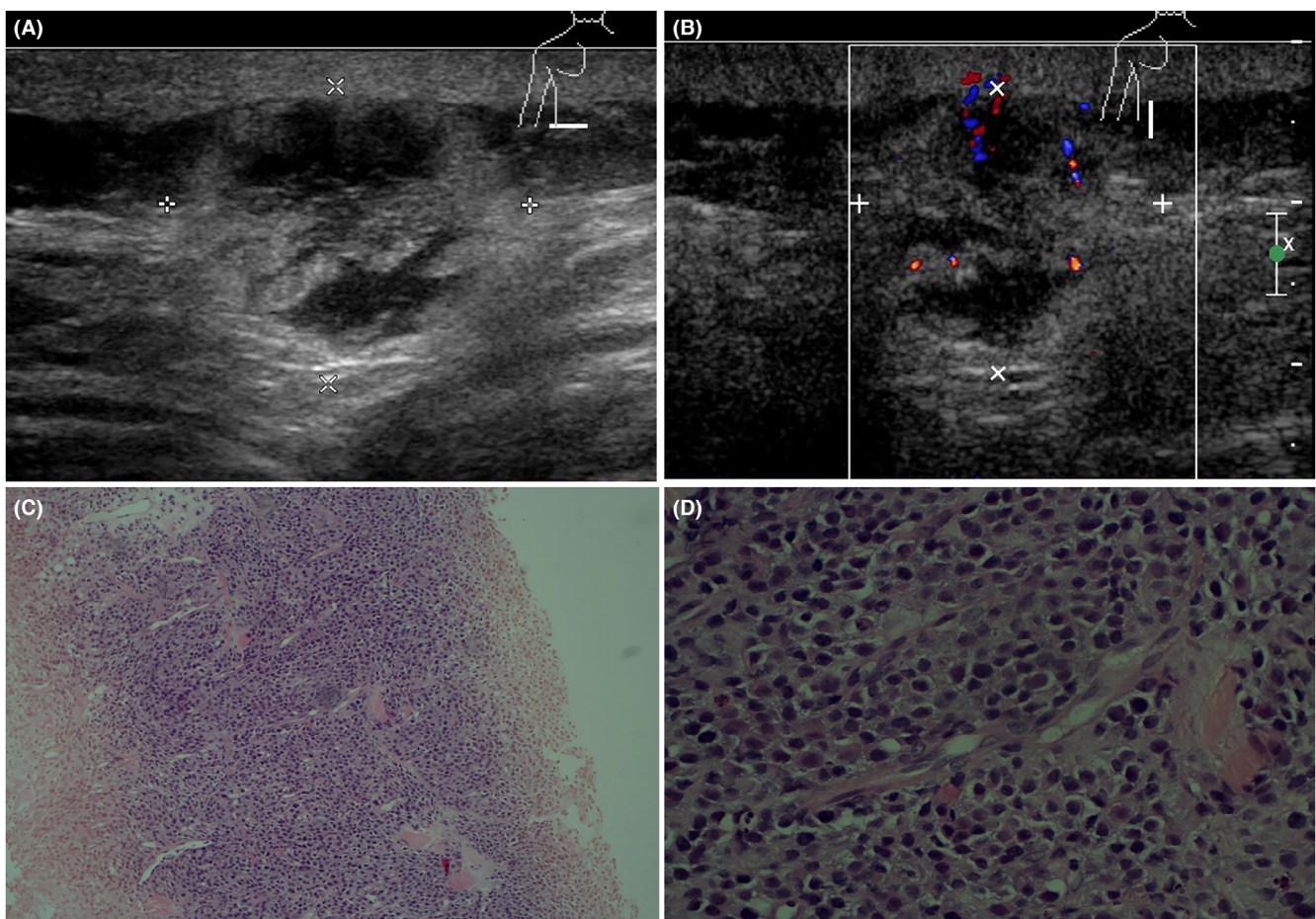


FIGURE 2 Multiple myeloma involving the lower back in a 66-year-old man (case 2): (A) Sonogram shows hypoechoic foci within a hyperechoic background on the lower back. (B) Color Doppler sonogram shows abundant vascularity. (C, D) Biopsy specimen (hematoxylin–eosin, original magnification 100, 400) of the areas predominantly hypoechoic echogenicity appears as dense plasmacytoid cells cluster.

median survival time was 13.5 months after skin involvement (8–36 months). Nodules were found in all patients. Two patients had multiple papules and plaques in the trunk and extremities simultaneously.

3.2 | Ultrasound findings

We summarized the sonographic findings of all patients in Table 1. Three patients presented with one lesion, four with two lesions, and

three with more than two lesions. Seven lesions were located in the trunk, involving the abdominal wall, chest wall, or lower back. The other lesions were found in the extremities, including thigh, forearm, upper arm, and foot. The lesions ranged from 1.2 to 8.3 cm in size. The lesions occurred in the skin and subcutaneous fat layer (four patients), subcutaneous fat layer (four patients), muscular layer, and subcutaneous fat layer (one patient), and skin (one patient). A total of 10 lesions involved subcutaneous fat tissue. A total of 10 lesions showed hypoechoic foci with a hyperechoic background (Figures 1

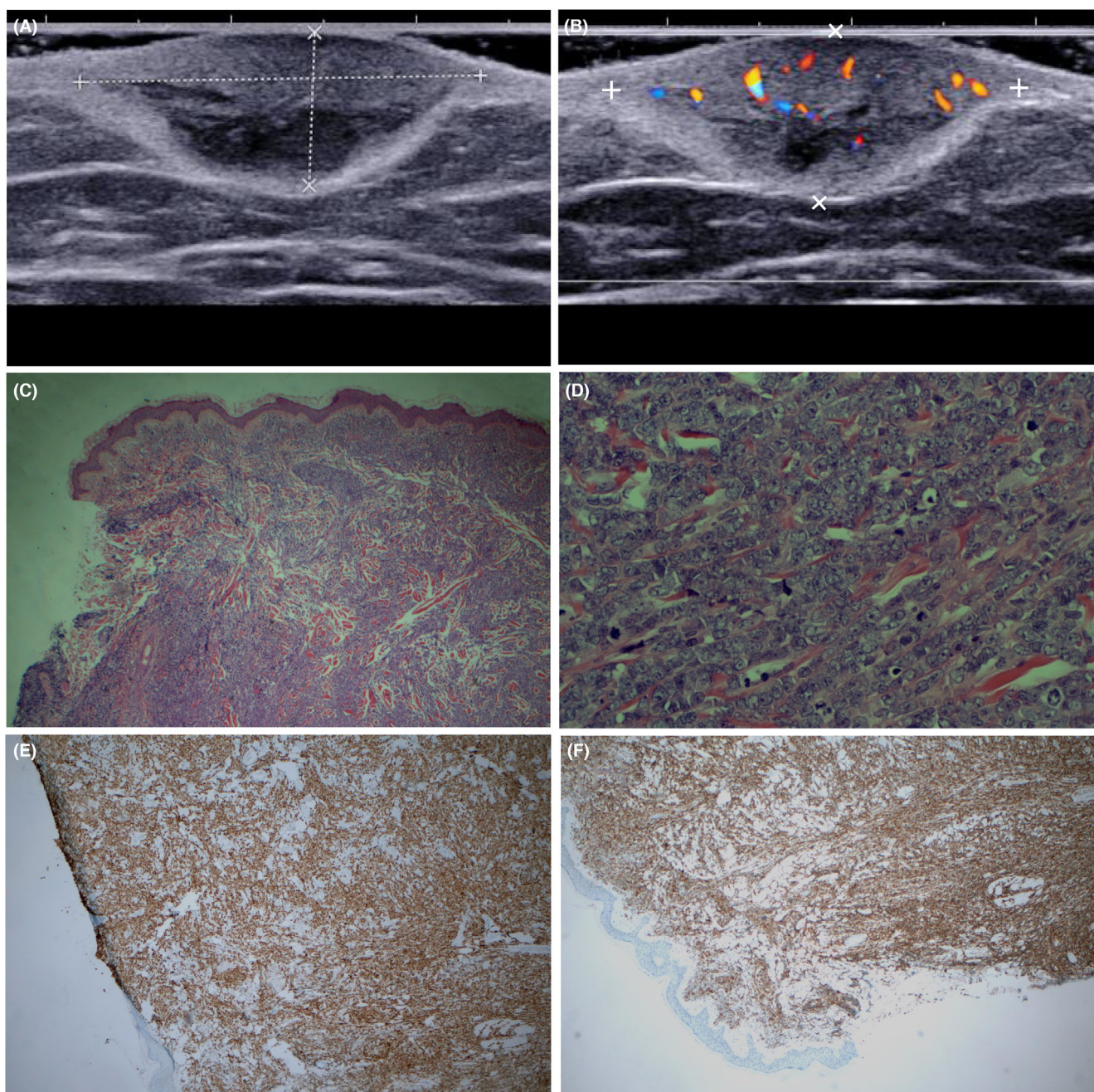


FIGURE 3 Leukemia involving the right thigh in an 27-year-old woman (case 4): (A) Sonogram shows a hypoechoic mass mainly located in the dermis. (B) Color Doppler sonogram shows abundant vascularity. (C, D) Biopsy specimen (hematoxylin–eosin, original magnification 50, 400) shows the areas of lower echogenic feature where B-lymphoblastic cells are more densely distributed. (E, F) The immunohistochemical staining for CD20, CD34, Ki-67, and TDT show that cellular infiltrates contain large numbers of CD34+ and TDT+ ($\times 50$).

and 2), and the other three lesions appeared hypoechoic (Figure 3). Vascularity was minimal in 1 lesion and abundant in 12 lesions.

3.3 | Comparison of ultrasound and histopathologic findings

In this study, we additionally assessed the histopathologic components. Biopsied areas dominated by hyperechoic showed that tumor cells clustered in a background of adipocytes (Figure 1). While areas predominantly hypoechoic echogenicity appeared as dense tumor cells clustered (Figure 2). Similarly, areas where the tumor cells were more densely distributed showed lower echogenic features (Figure 3).

4 | DISCUSSION

Hematologic neoplasms can present as specific secondary cutaneous lesions. Patients were first diagnosed with systemic hematologic neoplasms in most cases and may subsequently develop cutaneous neoplasms. The findings in our study were remarkable for the high percentage of cases presenting as nodular (100%). Two patients had papules and plaques along with nodules. In the study by Rebeca et al.⁸ nodules (36.7%) were the predominant findings in patients with hematological neoplasms, followed by plaques (18.4%), papulo-nodular (12.2%), and papules (12.2%). The selection of patients in our study may be biased, as it was limited to the condition that patients' lesions were palpable, potentially inaccurately showing the true incidence of cutaneous manifestation. In our study, most patients presented with multiple lesions (≥ 2) of skin and subcutaneous tissue, consistent with the previous research.⁸

We evaluated the sonographic findings and found 10 lesions containing hypoechoic foci within a hyperechoic background, and the other three lesions appeared hypoechoic. Hypoechoic foci within a hyperechoic background were similar to the ultrasonic performance of segmental panniculitis.¹² There were few case reports describing ultrasound imaging findings of subcutaneous lesions infiltrated by hematologic neoplasms.¹³⁻¹⁶ On ultrasound, the lesions within the subcutaneous fat layer appeared as linear hypoechoic areas within diffuse hyperechogenicity (i.e., panniculitis-like echo texture).¹³ The hyperechoic background may be due to tumor cell infiltration in the subcutaneous fat layer, which increased the number of reflecting interfaces. Local aggregation of tumor cells which had similar size and shape, resulted in reduced acoustic impedance, and appeared hypoechoic. In the study by Chiou et al. 11 of 12 cases in primary peripheral soft tissue lymphoma showed relatively homogeneous hypoechogenicity. The area of lymphocyte proliferation had less interface density than was needed to reflect the sound beam, which resulted in hypoechogenicity.¹⁷ However, in our study, only one of the four subcutaneous tissue lesions secondary to lymphoma was hypoechoic, while the rest contained hypoechoic foci within a hyperechoic background.

Our color Doppler images showed 12 masses with abundant vascularity, and one mass with minimal vascularity, which was concordant with primary peripheral soft tissue lymphoma in the previous research.¹⁷

There are several limitations to this study. First, the small sample size limited the evaluation of more useful ultrasound imaging features. Second, when patients had multiple lesions, not all the lesions were confirmed by pathology. Finally, further comparison study is needed between soft tissue infiltrated by hematologic neoplasms and other skin and subcutaneous tissue disorders such as panniculitis.

In conclusion, secondary involvement of skin and subcutaneous tissues by hematologic malignancies often present with multiple palpable masses showing the following ultrasound features: (1) subcutaneous fat infiltration, (2) hypoechoic foci with a hyperechoic background, and (3) abundant vascularity.

FUNDING INFORMATION

The Science Technology and Innovation Commission of Shenzhen Municipality in China (grant no. JCYJ 20210324110015040), The Shenzhen Key Medical Discipline Construction Fund (grant no. SZXK051), Financial Support of The Guangdong High-level Hospital Construction Fund (grant no. GD2019260), and The Shenzhen Virtual Reality Clinical Application Public Service Platform Promotion Project (grant no. XMHT20190104001).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Heng Lyu  <https://orcid.org/0000-0003-0041-9189>

De Sheng Sun  <https://orcid.org/0000-0003-0328-1197>

REFERENCES

- Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the haematological malignancy research network. *Br J Cancer*. 2011;105:1684-1692.
- Li AW, Yin ES, Stahl M, et al. The skin as a window to the blood: cutaneous manifestations of myeloid malignancies. *Blood Rev*. 2017;31:370-388.
- Merlo G, Cozzani E, Canale F, et al. Cutaneous manifestations of hematologic malignancies the experience of an Italian dermatology department. *Hematol Oncol*. 2019;37:285-290.
- Woo YR, Kim JS, Lim JH, et al. Prevalence and clinicopathologic characteristics of multiple myeloma with cutaneous involvement: a case series from Korea. *J Am Acad Dermatol*. 2018;78:471.e4.
- Lee WJ, Won KH, Won CH, et al. Secondary cutaneous lymphoma: comparative clinical features and survival outcome analysis of 106 cases according to lymphoma cell lineage. *Br J Dermatol*. 2015;173:134-145.
- Pamuk GE, Ak R, Tasci M, et al. Clinical characteristics of haematological malignancy patients diagnosed with leukaemia cutis: experience of a single centre. *Australas J Dermatol*. 2015;56:116-119.
- Calado R, Relvas M, Morgado F, et al. Specific cutaneous infiltrates in patients with haematological neoplasms: a retrospective study with 49 patients. *Australas J Dermatol*. 2021;62:e228.

8. Maitre E, Le-Page AL, Comoz F, et al. Usefulness of flow cytometry for the detection of cutaneous localization in malignant hematologic disorders. *Cytometry B Clin Cytom*. 2019;96:283-293.
9. Lee IS, Song YS, Lee SH, et al. Imaging analysis of superficial soft tissue lymphomas. *Clin Imaging*. 2018;49:111-116.
10. Genovese G, Nazzaro G, Alberti Violetti S, et al. Rosacea-like cutaneous localization of small lymphocytic lymphoma unmasked by high-frequency-ultrasound. *Skin Res Technol*. 2018;24:701-703.
11. Adler DD, Carson PL, Rubin JM, et al. Doppler ultrasound color flow imaging in the study of breast cancer: preliminary findings. *Ultrasound Med Biol*. 1990;16:553-559.
12. Román J, Giavedoni P, Roé E, et al. Inter- and intra-rater agreement of dermatologic ultrasound for the diagnosis of lobular and septal panniculitis. *J Ultrasound Med*. 2020;39:107-112.
13. Kang BS, Choi SH, Cha HJ, et al. Subcutaneous panniculitis-like T-cell lymphoma: US and CT findings in three patients. *Skeletal Radiol*. 2007;36:S67-S71.
14. Rodríguez Bandera AI, Moreno Bonilla G, Feito Rodríguez M, et al. Usefulness of high-frequency ultrasonography in the assessment of cutaneous lesions in children with hematologic malignancies. *Pediatr Dermatol*. 2018;35:e276-e280.
15. Fujii Y, Shinozaki T, Koibuchi H, et al. Primary peripheral T-cell lymphoma in subcutaneous tissue: sonographic findings. *J Clin Ultrasound*. 2004;32:361-364.
16. Polańska A, Dańczak-Pazdrowska A, Olek-Hrab K, et al. High-frequency ultrasonography – New non-invasive method in assessment of skin lymphomas. *Skin Res Technol*. 2018;24:517-521.
17. Chiou HJ, Chou YH, Chiou SY, et al. High-resolution ultrasonography of primary peripheral soft tissue lymphoma. *J Ultrasound Med*. 2005;24:77-86.

How to cite this article: Lyu H, Chen XM, Yu GY, et al. Sonographic features of secondary involvement of skin and subcutaneous tissues by hematologic malignancies. *J Clin Ultrasound*. 2022;50(9):1436-1442. doi:[10.1002/jcu.23368](https://doi.org/10.1002/jcu.23368)