

**Case Report**

Leukemia Cutis and Second Primary Malignant Melanoma: An Extraordinary Case Report

Banu Yaman¹, Nazan Özsan¹, Nisar Karadeniz¹, Tuğrul Dereli², Taner Akalın¹, Gülşen Kandiloğlu¹

¹Department of Pathology, Ege University Faculty of Medicine, Turkey

² Department of Dermatology, Ege University Faculty of Medicine, Turkey

Abstract

Introduction: Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukemia of adult. Patients with CLL/SLL are at higher risk for secondary malignancies such as skin, breast or lung tumours. Cutaneous infiltrates of CLL/SLL have been reported in association with squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and actinic keratosis.

Case Presentation: We present a patient with a previous history of CLL/SLL who developed a primary skin melanoma in the same area of leukemic infiltration, with the histological and immunohistochemical features.

An 80-year-old man presented with an 3 cm nonpigmented, erythematous and ulcerated plaque on the abdomen. Microscopically, a primary melanoma with an ulcer and skin infiltration of CLL/SLL at the ulcer base was seen.

Conclusion: Secondary cutaneous neoplasms can develop in patients with CLL/SLL and CLL/SLL infiltration can be associated with melanoma as in our case. The finding of a dense infiltrate of lymphocytes in cutaneous tumors should raise possibility of CLL/SLL and lead to a detailed examination.

Keywords: Skin; Melanoma; Chronic lymphocytic leukemia/small lymphocytic lymphoma; CD20; HMB-45

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***Correspondence to:** Banu Yaman, Department of Pathology, Ege University Faculty of Medicine, Turkey; Email: drbanuyaman@yahoo.com

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukemia of adults in Western countries. It is predominantly a disease of elderly patients and most are asymptomatic at the time of diagnosis.

Patients with CLL/SLL are at greater risk for other malignancies [1,2]. Skin, prostate, breast, lung tumours, melanoma, and lymphoma are examples for the second primary tumours encountered in patients with CLL/SLL. These tumors usually do not share the same site with CLL/SLL infiltrations [2]. Cutaneous infiltrates of CLL/SLL have been reported mostly in association with squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and actinic keratosis.

We present a patient with skin involvement of CLL/SLL in which primary melanoma was observed. To the best of our knowledge, these findings represent the first reported case of CLL/SLL skin infiltration together with a primary melanoma occurring at the same place.

Case presentation

An 80-year-old male with a history of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) presented with 3 cm nonpigmented, erythematous, infiltrated and ulcerated plaque on the abdomen. The patient stated the lesion had been present for three years. Clinically, the lesion was suspected to be skin infiltration of CLL/SLL. There was no personal or family history of melanoma. A shave biopsy was obtained.

Microscopic examination at scanning view revealed an ulcer on the surface and a dense infiltration of monotonous small lymphocytes at the bottom. On higher magnification, increased vascularization and neutrophilic infiltrate was seen at the base of ulcer and a spindle cell tumor was noticed between this inflammatory reaction and deep dermal infiltrate (Fig. 1).

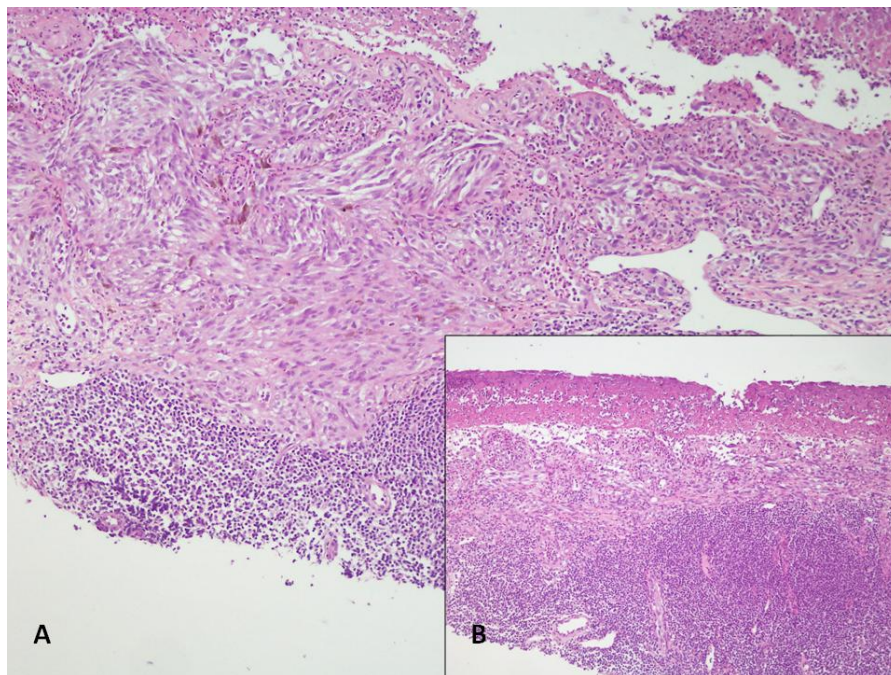


Figure 1 Ulcerated melanoma on the surface and dense infiltration of chronic lymphocytic leukemia/small lymphocytic lymphoma at the shave biopsy (**1A**: H&E x100, **1B**: H&E x40)

This tumour cells were composed of enlarged hyperchromatic nuclei and spindle or epitheloid cytoplasm and were found to be associated with confluent atypical melanocytes placed at the basal layer of the epidermis. Pagetoid spread was seen as single cells or cell groups and loss of cohesion was present in junctional nests. Squamous metaplasia in eccrine ducts was also present. The immunohistochemical profile revealed strong positivity for S100 and HMB-45 in the spindle cells near the ulcer.

CD20, CD5, bcl-2 and CD23 highlighted dense infiltration of small lymphocytic cells at the bottom of the lesion. CD3, CD10 and cyclin D1 were negative in these cells (Fig. 2).

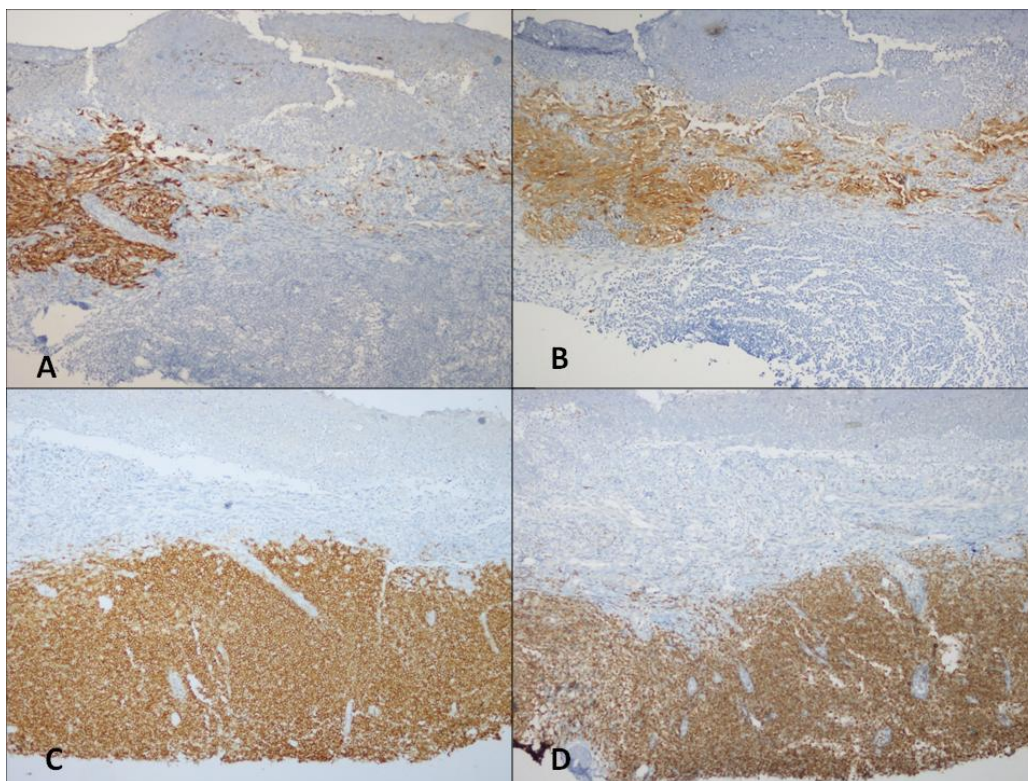


Figure 2A: HMB-45 positivity, **2B:** S100 positivity in melanoma cells, **2C:** CD20 and **2D:** bcl-2 positivity in leukemic cells (x40)

Based on the above-described morphological and immunohistochemical features, the dense lymphoid infiltration was interpreted as CLL/SLL infiltration and the accompanying spindle cell tumour was interpreted as a melanoma.

The patient was treated with wide local excision and an axillary lymph node was excised. Grossly, a 2.1 cm, poorly circumscribed, tan-brown lesion was seen with a centrally located ulcer (Fig. 3).

Sections stained with hematoxylin and eosin showed broad proliferation of melanocytes with enlarged hyperchromatic nuclei on the surface. The melanocytes were arranged as solitary units and nests along the dermal epidermal junction. Foci of invasion were seen at the dermal part. Dense leukemic infiltration was seen along the tumour at the bottom of the melanocytic lesion. The thickness of the melanoma was 0.77 mm, and the Clark stage was III.

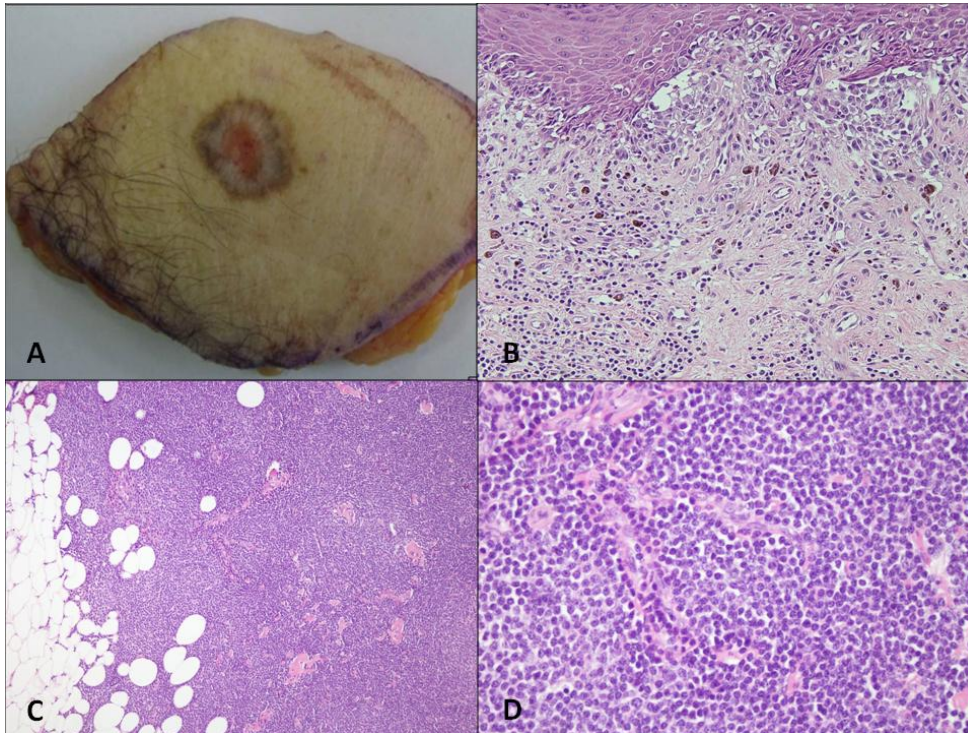


Figure 3A: Poorly circumscribed, tan-brown tumor with a centrally located ulcer, **3B:** Tumor at the excision material (H&E x200), **3C-3D:** Chronic lymphocytic leukemia/small lymphocytic lymphoma at the axillary lymph node (H&E x40 and x200).

No melanocytic tumor metastasis was seen in the axillary lymph node, but the lymph node architecture was totally effaced with small lymphoid cell infiltration consistent with CLL/SLL (Fig. 3), both morphologically and immunophenotypically with CD20, CD5, CD23 and bcl2 positivity.

Discussion

Chronic lymphocytic leukemia/small lymphocytic lymphoma is the most common leukemia of adults in western countries. It usually has an indolent clinical course and most patients are asymptomatic. The incidence rate increases with age with a mean age of 65 years at diagnosis [3]. Malignant melanoma, however, is a primary tumour of the skin that can indicate a highly aggressive prognosis with regard to its clinical and histological characteristics, and with a high incidence of local or distant metastasis. Its prevalence also increases in older ages.

Second primary malignancies can be found in patients with a primary tumour [1]. Different secondary tumours can be seen in cases with CLL/SLL prior to or following the disease. The prevalence has been reported as 10-20% in the literature. Skin, prostate, breast, and lung tumours, melanoma, lymphoma, and gastrointestinal tumours are some examples of second primary tumours [1, 2, 4].

Adami *et al.* [5] studied a total of 560000 patients including approximately 174000 cases with CLL/SLL and reported that CLL/SLL patients had a relative melanoma risk of 3.1. Landgren *et al.* [6] determined the relative melanoma risk as 1.19 in 7764 patients with CLL/SLL in their study in which 41181 lymphoma cases were screened in terms of secondary malignancies. In a survey carried out in 12452 patients with non-Hodgkin Lymphoma, Brennan *et al.* [7] established

melanoma as a secondary tumour in 93 cases and stated its standardized incidence ratio as 2.38. Brennan *et al.* [8] emphasized that melanoma could be seen as a second primary malignancy in CLL/SLL patients, and also that CLL/SLL could be the second primary in melanoma patients.

Distinct secondary tumours can be observed in patients with melanoma. Tumour types other than lymphoma with proven association with melanoma in the same patient are breast and prostate tumours and colorectal carcinomas [9-11]. Community-based studies have shown an increased incidence of secondary CLL/SLL in patients with metastatic melanoma [12, 13]. Melanoma may occur, before, at the same time, or after the lymphoma [4-8, 12-14].

Verwer *et al.* [14] evaluated 18226 cases with melanoma and found 55 patients (0.3%) who had lymphoma together with melanoma. The most common subtype was chronic lymphocytic leukemia/small lymphocytic lymphoma (49.1%). Lymphoma was diagnosed subsequent to melanoma in 41.8% patients, prior to melanoma in 12.7% patients, and concurrently with melanoma in 45.5%.

Farma *et al.* [2] presented 52 melanoma cases with chronic lymphocytic leukemia (CLL). The presence of melanoma was determined before the CLL diagnosis had been made in 32 cases (62%), and after the CLL diagnosis in 7 cases. In the same study, 22 patients (42%) had CLL on sentinel lymph node biopsy for their melanoma, and 5 of them had evidence of collision of metastatic melanoma and CLL in the sentinel lymph node [2].

A number of hypotheses have been suggested as the reason for the association of melanoma and lymphoma (CLL/SLL). One is that frequent and comprehensive follow-up of patients for the primary tumour can lead to an increased incidence of secondary malignancies [4]. The second is that both melanoma and CLL/SLL cells show abnormalities in chromosome 9p21 [4, 15]. Another assumption is that the impairment of lymphocyte-macrophage response can be a potential reason in patients with immunodeficiency [15]. Environmental factors such as sunrays, and distinct chemical products have also raised the incidence of melanoma and different lymphoma types. Ultraviolet light reduces T cell activity in various ways and promotes the incidence of lymphoma and other skin malignancies [4, 5, 15].

The present case is an example of cutaneous melanoma appearing after a 4-year history of CLL/SLL. The difference of our case from the others in literature was the observation of dense leukemic infiltration masquerading as melanoma clinically and histologically at first glance at the base of the leukemic infiltration.

There are a few articles on two different tumours occurring at different periods, and also case reports concerning melanoma metastasis and CLL/SLL infiltration in the same lymph nodes in the literature [2, 4-8, 12-14].

The lesions known as leukemia cutis can be traced in hematological malignancies such as leukemic skin infiltration, myeloid sarcoma or granulocytic sarcoma composed of granulocytic or monocytic precursor cells, B- or T- cell lymphoblastic lymphomas or CLL/SLL [16, 17]. Specific skin lesions in CLL/SLL can emerge with particular clinicopathological features in the form of solitary, localized or generalized papules, nodules or plaques due to distinctive underlying diseases [18]. Although direct skin infiltration is rare in patients with CLL/SLL, it can be seen in inflammatory or neoplastic lesions in the skin areas with chronic antigenic stimulation [16, 19] such as inflammatory conditions, infectious diseases such as *Borrelia* and Herpes or primary epithelial neoplasia [16, 18, 20-22]. Skin involvement of CLL/SLL extending from cutaneous epithelial tumours to SCC, BCC and actinic keratosis has been defined in a limited number of articles as case reports [19, 20, 23]. These leukemic infiltrations are in the form of grouped small, monotonous lymphocytes in the dermis adjacent to skin tumour [23]. It is reported that malignant lymphocytes

come to the tumoral area as a host response to the secondary tumour and do not aggravate the prognosis of the patient in terms of lymphoma [19, 20].

No other kind of skin lesion was determined in our 80-year-old patient with a history of CLL/SLL. Observation of leukemic infiltration intensifying around the melanoma that developed afterwards supports the mechanisms stated in the preceding literature. Leukemic infiltration around non-melanomatous tumours has been described in articles. However, there is no typical reference concerning intensive leukemic infiltration developing around a melanoma as seen in our case.

Conclusion

We presented a CLL/SLL patient with skin infiltration, diagnosed also as primary melanoma in the same area and with same biopsy, which has not been encountered in the literature previously to the best of our knowledge. Considering that secondary malignancies may occur in cases with CLL/SLL, the likelihood should also be assessed in the follow-up with biopsies of the cases in question. Care must be taken during the histopathological evaluation in this respect and further verification obtained by immunohistochemical analysis when suspicion exists.

Consent

We confirm that the patient has given their informed consent for the case report to be published.

References

1. Tsimberidou AM, Wen S, McLaughlin P, O'Brien S, Wierda WG, Lerner S, Strom S, Freireich EJ, Medeiros LJ, Kantarjian HM, Keating MJ. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol*. 2009, 27:904-910
2. Farma JM, Zager JS, Barnica-Elvir V, Puleo CA, Marzban SS, Rollison DE, Messina JL, Sondak VK. A collision of diseases: chronic lymphocytic leukemia discovered during lymph node biopsy for melanoma. *Ann Surg Oncol*. 2013, 20:1360-1364
3. Rozman C, Montserrat E. Chronic lymphocytic leukemia. *N Engl J Med*. 1995, 333:1052-1057
4. Cahill RA, McGreal G, Neary P, Redmond HP. Synchronous high-risk melanoma and lymphoid neoplasia. *Melanoma Res*. 2001, 11:517-522
5. Adami J, Frisch M, Yuen J, Glimelius B, Melbye M. Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *BMJ*. 1995, 310:1491-1495
6. Landgren O, Pfeiffer RM, Stewart L, Gridley G, Mellekjær L, Hemminki K, Goldin LR, Travis LB. Risk of second malignant neoplasms among lymphoma patients with a family history of cancer. *Int J Cancer*. 2007, 120:1099-1102
7. Brennan P, Coates M, Armstrong B, Colin D, Boffetta P. Second primary neoplasms following non-Hodgkin's lymphoma in New South Wales, Australia. *Br J Cancer*. 2000, 82:1344-1347
8. Brennan P, Scđo G, Hemminki K, Mellekjær L, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliever EV, Tonita JM, Seow A, Pompe-Kirn V, Martos C, Jonasson JG, Colin D, Boffetta P. Second primary cancers among 109 000 cases of non-Hodgkin's lymphoma *Br J Cancer*. 2005, 93:159-166
9. Bhawan J, Mehregan AH, Jung-Legg Y, Gellis SE. Pigmented basal cell carcinoma and superficial spreading malignant melanoma: an unusual combination. *J Cutan Pathol*. 1984, 11:471-475
10. Braun Falco M. Combined malignant melanoma and basal cell carcinoma tumor of the intermingled type. *J Cutan Pathol*. 2007, 34:731-735

11. Papa G, Grandi G, Pascone M. Collision tumor of malignant skin cancers: a case of melanoma in basal cell carcinoma. *Pathol Res Pract.* 2006, 202:691-694.
12. Cantor AS, Moschos S, Jukic DM. A principal case of multiple lymphoid collision tumors involving both B-cell chronic lymphocytic leukemia and metastatic malignant melanoma. *Dermatol Online J.* 2010, 16:6
13. McKenna DB, Stockton D, Brewster DH, Doherty VR. Evidence for an association between cutaneous malignant melanoma and lymphoid malignancy: a population-based retrospective cohort study in Scotland. *Br J Cancer.* 2003, 88:74-78
14. Verwer N, Murali R, Winstanley J, Cooper WA, Stretch JR, Thompson JF, Scolyer RA. Lymphoma occurring in patients with cutaneous melanoma. *J Clin Pathol.* 2010, 63:777-781
15. McKenna DB, Doherty VR, McLaren KM, Hunter JA. Malignant melanoma and lymphoproliferative malignancy: is there a shared aetiology? *Br J Dermatol.* 2000, 143:171-173
16. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F. Leukemia cutis. *Am J Clin Pathol.* 2008, 129:130-142
17. Cerroni L, Zenahlik P, Höfler G, Kaddu S, Smolle J, Kerl H. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. *Am J Surg Pathol.* 1996, 20:1000-1010
18. Cerroni L, Höfler G, Bäck B, Wolf P, Maier G, Kerl H. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia (B-CLL) at sites typical for *Borrelia burgdorferi* infection. *J Cutan Pathol.* 2002, 29:142-147
19. Smoller BR, Warnke RA. Cutaneous infiltrate of chronic lymphocytic leukemia and relationship to primary cutaneous epithelial neoplasms. *J Cutan Pathol.* 1998, 25:160-164
20. Agnew KL, Ruchlemer R, Catovsky D, Matutes E, Bunker CB. Cutaneous findings in chronic lymphocytic leukaemia. *Br J Dermatol.* 2004, 150:1129-1135
21. Doutre MS, Beylot-Barry M, Beylot C, Dubus P, Lafont ME, Belleannee G, Broustet A, Merlio JP. Cutaneous localization of chronic lymphocytic leukemia at the site of chickenpox. *J Am Acad Dermatol.* 1997, 36:98-99.
22. Robak E, Robak T. Skin lesions in chronic lymphocytic leukemia. *Leuk Lymphoma.* 2007, 48:855-865
23. Padgett JK, Parlette HL 3rd, English JC 3rd. A diagnosis of chronic lymphocytic leukemia prompted by cutaneous lymphocytic infiltrates present in mohs micrographic surgery frozen sections. *Dermatol Surg.* 2003, 29:769-771