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Lymphomatoid papulosis in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma: case report and literature review

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Abstract

Background: Chronic lymphocytic leukemia (CLL) is a B cell lymphoproliferative disorder that characteristically presents in older individuals. Small lymphocytic lymphoma (SLL) occurs when CLL cells infiltrate lymph nodes and other tissues but spare peripheral blood and bone marrow. Lymphomatoid papulosis (LyP) is an indolent cutaneous CD30+ lymphoproliferative disorder characterized by papules and nodules that develop and spontaneously regress over weeks to months.

Methods: An 84-year-old man with CLL who developed LyP is described. The features of other patients who concurrently had both of these conditions are reviewed.

Results: A man was diagnosed with CLL at age 50 years. At 84 years of age, he presented with red papules on his buttocks, which demonstrated a CD30+ lymphoproliferative disorder on biopsy. Correlation of the lesion history, morphology, and histopathology established the diagnosis of LyP. LyP and CLL/SLL, including in this patient, has only been reported in 11 individuals, to our knowledge.

Conclusion: The concurrent expression of LyP and CLL/SLL is rare. Since the conditions derive from different lymphocyte subsets, the concurrent expression may be merely coincidental. However, the development of both conditions in the same individual may provide additional insight into the pathogenesis of these disorders.

Keywords: chronic, leukemia, lymphocytic, lymphoma, lymphomatoid, papulosis, small

Introduction

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma is a B cell lymphoproliferative disorder that typically appears in individuals older than 60 years. Lymphomatoid papulosis (LyP) is a CD30+ lymphoproliferative disorder that is most commonly observed in patients in their sixth decade. However, it may also be seen in children and patients older than 60 years. A man with longstanding CLL who subsequently developed LyP is described and the features of other individuals with concurrent CLL and LyP are reviewed.

Case Synopsis

An 84-year-old man presented for evaluation of asymptomatic lesions on his buttocks. His medical history was significant for CLL diagnosed at age 50 years. Characterization of his leukemic cells revealed a common CLL phenotype, absence of ZAP-70 expression, and expression of a mutated IgVH gene with 89.5% homology to IgVH4-61. His CLL was assessed as being indolent stage I disease, for which he received periodic clinical monitoring and did not require leukemia-directed treatment.

Cutaneous examination revealed more than 100, 2-3mm, red flat-topped superficial follicular-based and non-follicular-based papules on the buttocks (**Figure 1**). The patient also had an upper respiratory infection. Clinical differential diagnosis included

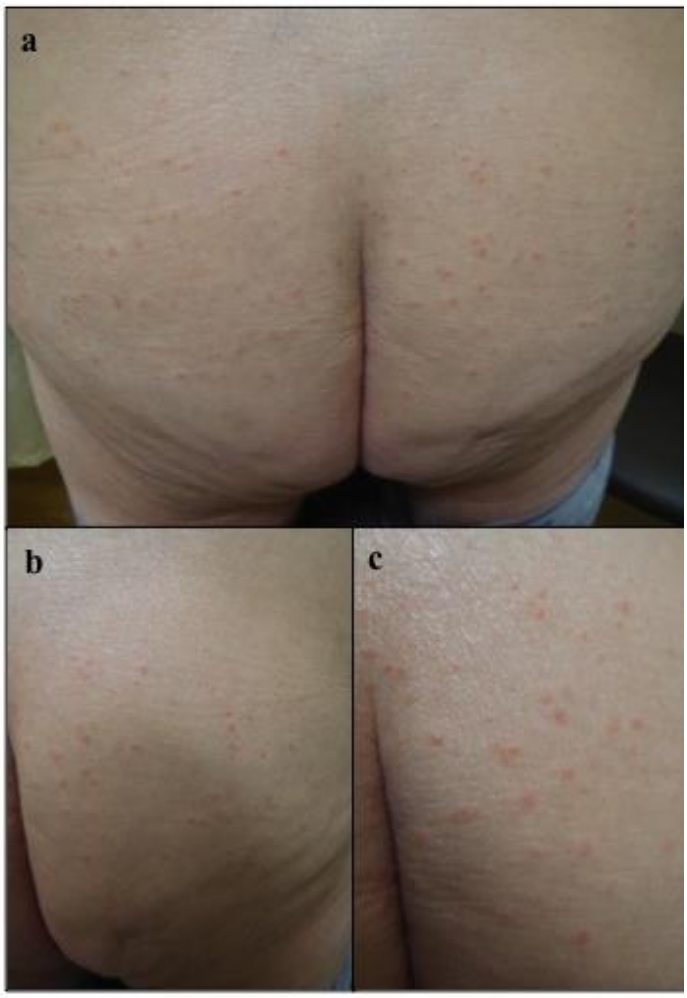

Figure 1. *Distant (**a**) and closer (**b, c**) views of lymphomatoid papulosis in a man with chronic lymphocytic leukemia presenting as red, flat-topped papules on the buttocks.*

folliculitis and viral exanthem. The patient declined biopsy; the buttocks were empirically treated for folliculitis with chlorhexidine solution 4% daily for ten days.

The patient returned for evaluation six months later. The buttock lesions were still present. In addition, new red papules with similar morphology were also noted on the right posterior thigh. Two lesions were biopsied.

Microscopic examination of both papules showed edema in the papillary dermis and a dense collection of lymphoid cells in the superficial dermis. Within the inflammatory infiltrate, there were scattered hyperchromatic and pleomorphic large cells (**Figure 2**). Membranous CD30 immunopositivity was present on several of the large cells (**Figure 3**). The

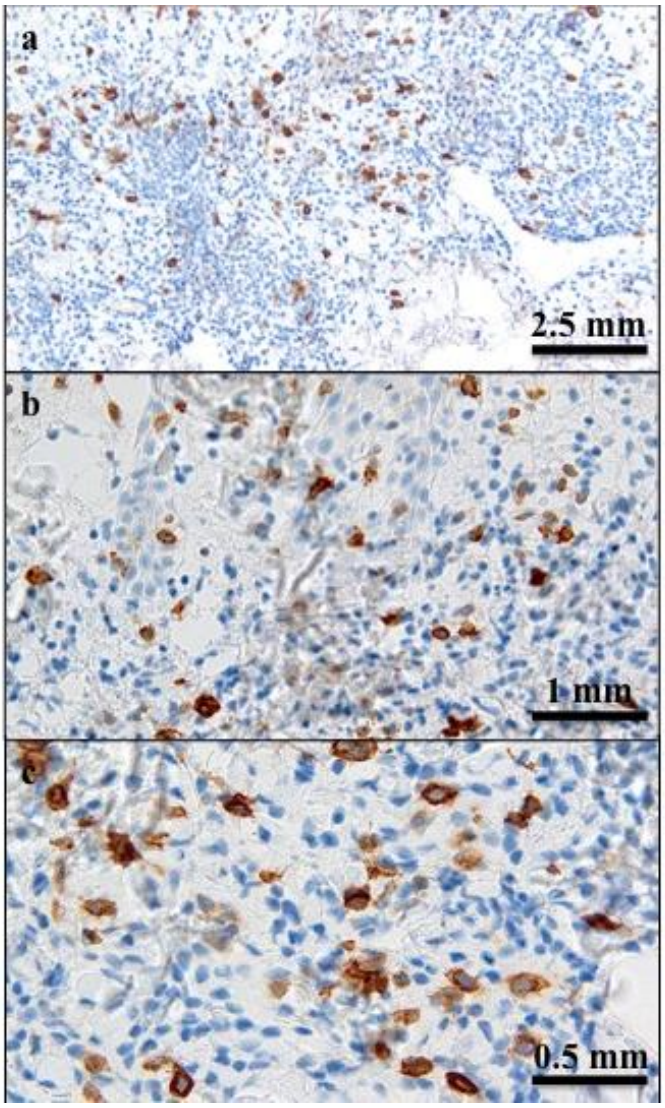

Figure 2. *Low (**a**) and higher (**b, c**) magnification views of the right buttock lesion shows a dense infiltrate of lymphocytes in the upper dermis. Some of the large lymphoid cells have enlarged atypical nuclei with mitoses. H&E, **a**, 4×; **b**, 10×; **c**, 20×.*

pathologic changes observed were those of a CD30+ lymphoproliferative disorder. Correlation of the history, clinical morphology, and pathologic changes established the diagnosis of LyP.

Topical therapy using clobetasol dipropionate 0.05% cream twice daily was initiated. Within two weeks, the papules had begun to resolve. After three weeks, no lesions were present and therapy was discontinued. The lesions recurred; within two weeks of restarting clobetasol dipropionate 0.05% cream twice daily, all the lesions resolved and have not reappeared (**Figure 4**).

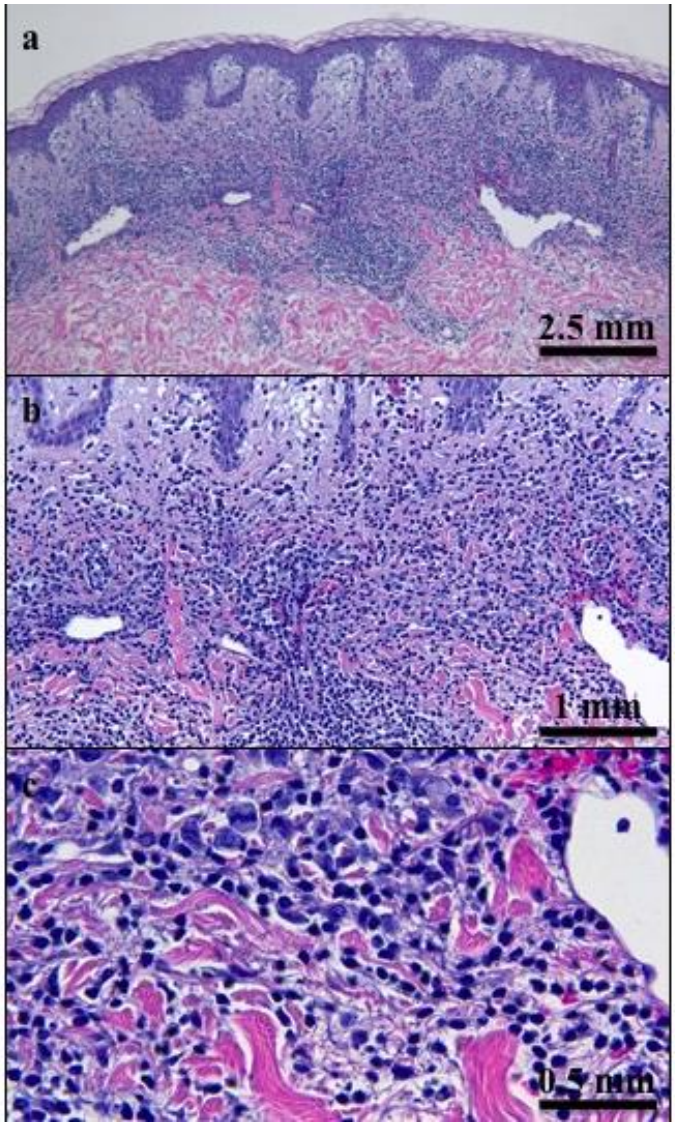

Figure 3. *Low (**a**) and higher (**b, c**) magnification views of CD30+ staining lymphocytes in the dermal inflammatory infiltrate, CD30 immunoreactivity, **a**, 10×; **b**, 10×; **c**, 20×.*

Case Discussion

CLL is a lymphoproliferative disease in which phenotypically mature malignant B lymphocytes progressively accumulate in the peripheral blood, bone marrow, and lymph nodes [1].For patients with early disease, observation and periodic follow-up may be performed until the disease progresses or becomes symptomatic [2]. Chemoimmunotherapy consisting of rituximab in combination with fludarabine and cyclophosphamide was the standard front-line treatment for CLL; currently, initial treatment may be with a newer agent: ibrutinib [1, 3].

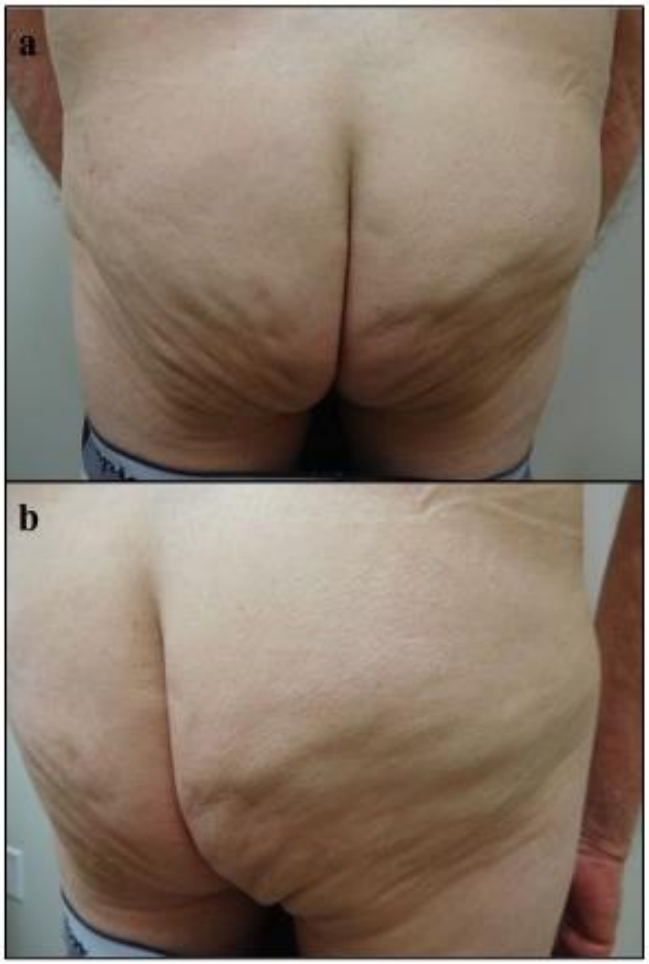

Figure 4. *Distant (A) and closer (B) view of buttocks showing complete resolution of lymphomatoid papulosis following topical therapy with clobetasol diproprionate 0.05% cream.*

The diagnosis of a cutaneous CD30+ lymphoproliferative disorder is made by finding CD30 antigen overexpression on large atypical T cells from a skin lesion biopsy. CD30+ lymphoproliferative disorders include anaplastic large cell lymphoma, classical Hodgkin lymphoma, and primary cutaneous CD30+ lymphoproliferative disorders such as mycosis fungoides and LyP [4]. The patient's history and the lesion morphology typically enable correlation of the pathology findings to determine the appropriate diagnosis.

LyP clinically presents as papules or nodules that may ulcerate, spontaneously regress, or both. The papules may resolve within four to eight weeks, whereas nodules may persist for several months before disappearing [5]. LyP was not initially suspected in our patient.

Table 1. *Epidemiology and location of lymphomatoid papulosis and chronic lymphocytic leukemia/small lymphocytic lymphoma*[a,b].

Case	Sex/Race	Age LyP[c]	Age CLL/SLL[d]	LyP Preceding/Following/Concurrent with CLL/SLL[e]	Location	Reference
1	Male/ND	63	55 CLL	Following, 8 years	Multifocal	13, Case 1
2	Male/ND	70	70 SLL	Concurrent	Face, Knee, Perianal	13, Case 3
3	Male/ND	72	64 CLL	Following, 8 years	Arms, Legs, Trunk	14
4	Female/ ND	76	70 CLL	Following, 6 years	ND	12
5	Female/ Caucasian	78	78 CLL	Concurrent	Back, Inguinal, Legs	15
6	Male/ND	78	67 CLL	Following, 11 years	Multifocal	13, Case 2
7	Male/ Caucasian	84	50 CLL	Following, 34 years	Buttocks	Current case

[a] Abbreviations. CLL, chronic lymphocytic leukemia; LyP, lymphomatoid papulosis; ND, not described; SLL, small lymphocytic lymphoma

[b] Cases 8-11 included 3 patients whose LyP occurred prior to diagnosis of CLL and 1 patient whose LyP followed the diagnosis of CLL; no additional details were described [11]

[c] The onset age, when the diagnosis of LyP was established, in years

[d] The onset age, when the diagnosis of CLL/SLL was established, in years

[e] The number of years that the diagnosis of LyP either preceded, followed, or was concurrent with the diagnosis of CLL; the diagnosis of LyP was considered to be concurrent with that of CLL if it occurred within the same year

Pathologic changes observed in LyP have been classified into six types: A, B, C, D, E, and LyP with 6p23.3 rearrangement [6-8]. Our patient's lesions had findings that were most consistent with type A. The pathologic features of type A LyP (the most common histologic type) are a dense dermal infiltrate of small lymphocytes containing scattered large CD30-positive cells with atypical mitoses [9].

The disease course of LyP is variable. The skin lesions can wax and wane; they can also resolve spontaneously. Potential therapeutic interventions — to provide symptomatic relief — include topical corticosteroids, psoralen and ultraviolet light therapy, and low-dose methotrexate. However, none of these modalities change the associated risk of lymphoma in LyP [10]. Our patient's lesions promptly resolved with high-potency corticosteroid application.

LyP may be associated with other lymphoproliferative disorders, most commonly mycosis fungoides and anaplastic large cell lymphoma [11]. LyP has also been associated with hematologic malignancies, including Hodgkin lymphoma, multiple myeloma, other gammopathies, and myelodysplastic syndrome [12].

LyP in patients with CLL/SLL, including our patient, has only been described in 11 individuals (**Tables 1, 2**), [12-15]. Demographic characteristics were available for seven of these patients, which included five men and two women. The patients were diagnosed with LyP at a median age of 76 years (range 63 to 84 years). They were diagnosed with CLL/SLL at a median age of 64 years (range 50 to 78 years).

The diagnosis of LyP either preceded (three patients), followed (six patients), or occurred concurrently with (two patients) the diagnosis of CLL/SLL. Therefore, in this group of 11 patients, the diagnosis of LyP followed the diagnosis of CLL a median of six years. However, when LyP followed the diagnosis of CLL/SLL (in the five patients in whom the duration of LyP was described), the hematologic dyscrasia had been diagnosed between six to 34 years earlier (median, eight years).

Table 2. *Lesion features and sequelae of patients with lymphomatoid papulosis and chronic lymphocytic leukemia/small lymphocytic lymphoma*[a,b].

Case	Symptoms	Morphology	Lesion number	Recurrence	Treatment	Response	Ref
1	Pruritus, scar formation	Papulo-necrotic lesions	>25	No	PUVA	Partial response	13, Case 1
2	ND	Single nodule	ND	Yes	Excision, topical carmustine	Complete response	13, Case 3
3	None	Nodules Plaques	Crops	Yes	Low-dose methotrexate	Complete response	14
4	ND	ND	ND	ND	ND	ND	12
5	Pruritus	Papules Plaques	Crops	Yes	Gabapentin, intralesional corticosteroids, methotrexate, topical corticosteroids	Partial response	15
6	Pruritus, scar formation	Papulo-necrotic lesions	ND	No	Oral corticosteroids	Partial response	13, Case 2
7	None	Papules	> 100	Yes	Topical corticosteroids	Complete response	Current case

[a] Abbreviations. ND, not described; PUVA, psoralen-ultraviolet A light therapy; Ref, reference; >, greater than.
[b] Cases 8-11 included 3 patients whose LyP occurred prior to diagnosis of CLL and 1 patient whose LyP followed the diagnosis of CLL; no additional details were described [11]

The most common presentation of LyP in CLL/SLL patients was a papular eruption. However, some of the patients' lesions were plaques and nodules. They were usually located on trunk and extremities.

Recurrence of LyP occurred in three men, including our patient, and one woman. In our patient, all of the lesions resolved within three weeks after he began to apply high-potency corticosteroids. When his LyP recurred after stopping therapy, all of the lesions promptly rapidly cleared when the topical corticosteroid treatment was again initiated; in addition, there has been no subsequent recurrence.

Management of LyP has been variable, including carmustine, corticosteroids (intralesional, systemic, or topical), excision, gabapentin, methotrexate, and psoralen and ultraviolet light therapy. The response to LyP treatment in CLL/SLL patients also varied. Half the patients (three of six) had a partial response and half the patients (three of six) had complete responses.

The coexistence of LyP, a T cell proliferative disease, and CLL/SLL, a B cell proliferative disease, is intriguing. Indeed, it may be merely coincidental and not associated with pathogenesis of the hematologic disorder. However, it has been postulated that LyP may develop after CLL/SLL owing to the immunodeficiency induced by the disease and the immunosuppressive therapies used to treat the condition [13].

Conclusion

LyP in patients with CLL/SLL is rare. To the best of our knowledge, it has been described in 11 adults, including our patient. The onset of LyP either preceded (three patients), followed (six patients) or appeared within the same year (two patients) as the diagnosis of CLL/SLL. Most lesions were papules. The management of LyP in these patients varied widely. The patients either experienced a partial (50%) or complete (50%) response of their LyP to treatment.

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