Granuloma annulare-like eruption in chronic lymphocytic leukemia

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Abstract

We report a patient with new-onset ulcerated granuloma annulare with concomitant involvement of B-cell leukemia. A granuloma annulare-like eruption with concomitant B cell chronic lymphocytic leukemia involvement in the skin is extremely rare, as only three cases have been previously reported in the literature to our knowledge. Given the rarity of ulceration in conventional granuloma annulare, it is possible this finding may serve as a diagnostic clue for underlying malignancy.

Keywords: granuloma annulare, granulomatous dermatitis, chronic lymphocytic leukemia, cutaneous leukemia, ulcer

Introduction

Granuloma annulare (GA) is a self-limited condition classically characterized by an asymptomatic eruption of annular, erythematous papules or plaques, most frequently affecting the distal extremities [1]. Ulceration is uncommon. Histopathological findings include interstitial or palisading histiocytes and lymphocytic infiltration in the dermis [1]. The pathogenesis has yet to be fully determined [2]. Although an association between GA and hematopoietic malignancies has been reported [3-13], GA-like infiltrates with concomitant involvement of B-cell chronic lymphocytic leukemia (B-CLL) in the same skin lesion is extremely rare [14,15]. We report a 75-year-old man who presented with an ulcerating GA-like eruption with cutaneous B-CLL co-involvement in association with systemic B-CLL progression.

Case Synopsis

A 75-year-old man with Rai stage I-II B-CLL presented to the dermatology clinic for evaluation of a new skin eruption. He had a 10-year history of B-CLL, for which he was monitored without treatment. One month prior to presentation, he developed approximately five erythematous papules and plaques, several with central ulceration, on the back and abdomen that progressively enlarged. The patient reported "irritation" of the lesions upon friction against clothing, though they were otherwise asymptomatic. Around the time of onset, the patient had acute bronchitis that was treated with doxycycline. Review of systems was negative for fever, chills, and night sweats.

Physical examination revealed five discrete 0.5cm–3.0cm mildly edematous, erythematous papules and plaques on the mid-back (**Figure 1**), flanks, and anterior left forearm. The larger plaques demonstrated central ulceration with fibrinous crust (**Figure 1**). Clinical differential diagnoses included Sweet syndrome, cutaneous involvement of leukemia/lymphoma, and granulomatous dermatitis.

Histopathology revealed a mixed inflammatory infiltrate composed mostly of interstitial histiocytes, many multinucleated and exhibiting elastophagocytosis, and moderately dense perivascular/periadnexal lymphocytes (**Figure 2**),

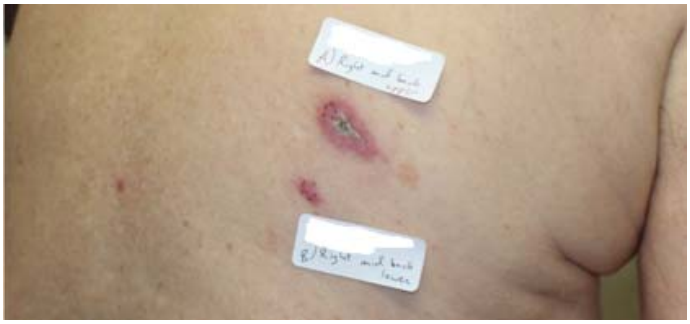

Figure 1. *Clinical findings. Physical examination revealed 0.5–3.0cm edematous, erythematous papule and plaque on the mid-back. The plaque demonstrated central ulceration with fibrinous crust.*

the vast majority of which were $CD20^+$ with variable CD5 co-expression.

A diagnosis of granuloma annulare-like dermatitis with concurrent cutaneous B-cell lymphocytic leukemia involvement was made. Upon 3-week follow-up, the lesions remained asymptomatic and the previously ulcerated lesions had re-epithelialized. The hematology-oncology department was consulted for evaluation and management of possible CLL progression. Within three months of initial presentation the patient developed systemic symptoms consisting of fever, night sweats, and fatigue, in association with progressively worsening lymphocytosis and cytopenia indicating systemic progression of his B-CLL.

Case Discussion

Although uncommon, cutaneous involvement by B-CLL may occur either as a primary leukemia cutis or as a secondary infiltrate associated with a separate neoplastic or inflammatory process [15-23]. The co-involvement of B-CLL with a GA-like infiltrate in the same cutaneous lesion is extremely rare [14,15]. To our knowledge, only three other cases have been reported (**Table 1**). One proposed mechanism for this unusual finding is that a granulomatous reaction may occur in response to locally infiltrating malignant lymphocytes [15]. Conversely, it is possible that neoplastic cells may be secondarily recruited to a site of primary dermatosis as a reactive inflammatory process [15]. For example, cutaneous B-CLL has been reported in healing varicella-zoster lesions [15,24,25]. In those cases, it is possible that Wolf isotopic response may have played a role, in which a specific cutaneous site that has been "immunocompromised" by a prior primary dermatosis may be subsequently affected by a secondary opportunistic pathology [25,26]. A similar phenomenon may be at play in our case.

In previously reported cases, patients with cutaneous co-involvement of granulomatous dermatitis and B-CLL presented with an eruption of erythematous, annular papules or plaques on the extremities or trunk [14,15]. In contrast, our patient

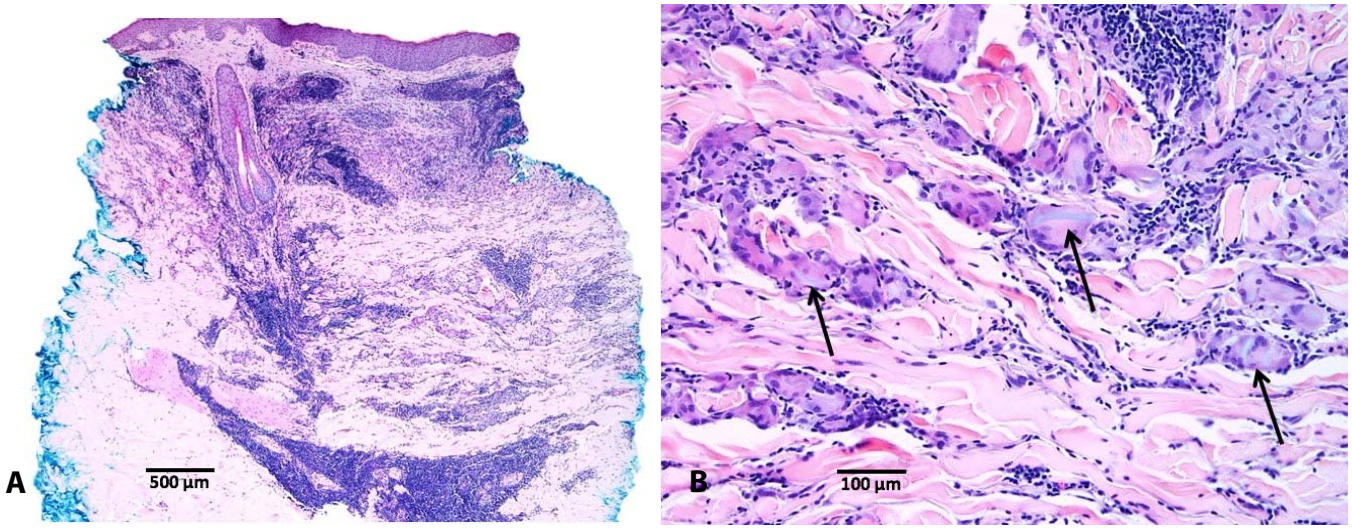

Figure 2. *Histopathology findings revealed **A)** interstitial histiocytes accompanied by a moderately dense perivascular/periadnexal lymphocytic infiltrate. H&E, 40×. **B)** On higher power, there are multinucleated histiocytes that demonstrate elastophagocytosis (arrows). H&E, 200×.*

Table 1. *Reported cases of concomitant granuloma annulare-like infiltrate and cutaneous involvement of B-CLL in same skin lesion.*

Patient [Ref]	Age/ Gender	B-CLL History	Location	Ulcerated	Elastophagocytosis	Immunophenotype of atypical lymphocytes	Treatment & Outcome
1 [14]	73/Male	10 years; Rai stage IV	Upper extremities	No	Yes	CD5, CD43, CD20, CD79a	Topical steroid, antihistamine, oral cephalexin, griseofulvin → no response; chemotherapy → cleared within 3 mo
2 [15]	72/Male	4 years; Rai stage I-11	Trunk, upper extremities	No	No	CD5, CD20, CD79a	TAC 0.1% cream, narrow band UV, and MTX sodium (no chemotherapy) → no response by 12 mo follow-up
3 [15]	76/Male	2 years; Rai stage I	Left arm	No	No	CD5, CD20, CD79a	None → did not clear by 24 mo follow-up
4 [present case]	75/Male	10 years; Rai stage I-II	Abdomen, flank, left upper extremity	Yes	Yes	CD5, CD20	None → improved but not cleared at 3 week follow-up

Ref, reference; B-CLL, B-cell chronic lymphocytic leukemia; TAC, triamcinolone acetonide; UV, ultraviolet; MTX, methotrexate.

uniquely demonstrated plaques that evolved with ulcerations. Histopathology typically reveals interstitial or palisading multinucleated histiocytes admixed with perivascular, atypical, small lymphocytes with small nucleoli throughout the dermis [14,15]. Immunohistochemistry may demonstrate atypical lymphocytes predominately expressing B cell markers CD20 and CD79a, as well as aberrant co-expression of T cell markers CD5 and CD43 [14,15].

Interestingly, histopathology of our patient's back lesions revealed elastophagocytosis, which is more commonly observed in actinic granuloma or annular elastolytic granuloma typically in sun-exposed areas [1,14,27-29]. However, the main sites of involvement in our patient were not sun-exposed.

The skin eruption in our patient was followed by progressive systemic signs of B-CLL, suggesting a possible correlation between this cutaneous manifestation and the systemic progression of B-CLL, although this correlation has not been widely established. Only one of three other reported cases of concomitant B-CLL with a GA-like infiltrate also demonstrated systemic progression.

Interestingly, a previous case involving GA-like infiltrate with co-involvement of B-CLL reported clearance of the lesions after three months of chemotherapy [14], whereas cases of similar pathology that did not receive chemotherapy did not demonstrate resolution of the lesions [15]. Thus, chemotherapy may be an effective option for treating the GA-like lesions, in addition to the underlying malignancy, when presenting concomitantly with locally infiltrating malignant lymphocytes. Furthermore, these findings also indicate that a GA-like eruption in an elderly patient may suggest an underlying malignancy as a possible etiologic mechanism. Additional systemic diseases suggested to be associated with GA include diabetes mellitus, hyperlipidemia, sarcoidosis, Sweet

syndrome, thyroid disease, and infectious diseases including HIV/AIDS [2,30], highlighting the importance of a thorough clinical evaluation in patients with GA.

Conclusion

Granuloma annulare-like dermatitis with cutaneous B-CLL involvement is extremely rare and this is the first reported case with ulcerative morphology. Importantly, the eruption of GA-like lesions may indicate underlying malignancy. Owing to the association of GA with systemic disease, it is essential for clinicians to further investigate a GA-like eruption, particularly in the elderly, with a thorough review of systems and workup. In patients with a known history of CLL, clinical suspicion should be appropriately elevated.

Potential conflicts of interest

The authors declare no conflicts of interest.

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