Granulomatous dermatitis co-existing with cutaneous B cell lymphoma: Case report of an intriguing association

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DOI: https://doi.org/10.22271/27080056.2022.v4.i1a.46

Abstract
A Granulomatous lesion in the skin is a common finding and cutaneous lymphoma, although less common, is not a rare entity. However few case reports exist of cutaneous granulomatous lesion harboring a lymphoma. We present a case of a 72-year-old male, with no known co morbidities presenting with painless erythematous papules and nodules over the forehead, trunk and limbs since 10 days. The skin biopsy from the lesion showed few granulomas along with giant cells and a diffuse monomorphic population of lymphoid cells in the dermis reaching up to the subcutaneous fat. The atypical morphology was further worked up with extensive panel of immunohistochemistry markers which favored the diagnosis of low-grade cutaneous B cell lymphoma. Patient was worked up for systemic lymphoma and PET CT revealed multiple enlarged homogenously enhancing lymph nodes. A cervical lymph node confirmed a nodal B-cell lymphoma. We present this case for its rarity and how evaluation of skin biopsy in this case provided useful clues towards diagnosis of a systemic lymphoma.

Keywords: Cutaneous B cell lymphoma, granulomatous dermatitis, secondary cutaneous SLL

Introduction
Lymphomas are a heterogeneous group of malignancies that arise from the clonal proliferation of B- cell, T- cell and natural killer (NK) cell subsets of lymphocytes at different stages of maturation [1]. Cutaneous B cell lymphomas can be primary or secondary to systemic lymphomas. A prominent granulomatous reaction could be observed in 1.8% of all patients with cutaneous lymphoma (primary or secondary) [2]. Cutaneous lymphoma with prominent granulomatous reaction causes a major pitfall in the histopathological diagnosis. Many a times, prominent granulomatous lesion may obscure neoplastic lesion. We present a case of an elderly male with cutaneous lesions showing features of granulomatous lesion during initial examination and interesting revelations on further workup.

Case report
A 72-year-old male, with no prior comorbidities presented to dermatology OPD with painless erythematous papules and nodules over the forehead, trunk, and limbs with generalized lymphadenopathy of 10 days duration. (Fig 1a) A skin biopsy was performed with clinical suspicion of cutaneous B & T cell lymphoma, sarcoidosis, histiocytosis and histoid leprosy. On histopathological examination, the epidermis was thinned out with flattening of rete ridges. Dermis showed a diffuse, dense infiltrate of monomorphic population of lymphocytes with a subepidermal grenz zone and extending to the adnexal structures and subcutaneous fat. The lymphoid cells were small to intermediate in size with a round to oval, non-cleaved, hyperchromatic nucleus. Interspersed between these cells were collections of foamy histiocytes forming granulomas along with multinucleate giant cells. No epidermotropism, angiogenesis, features of vasculitis were noted. No acid fast bacilli were seen on Ziehl Nelson stain (Fig 2 a-c).

On immunohistochemistry, the lymphoid cells were positive for CD20 with only scant reactive T cells showing CD3 positivity, confirming B cell origin. Ki-67 index showed high proliferation with 30% of the lymphoid cells showing strong nuclear staining. On further IHC workup these neoplastic cells were positive for CD5, CD23, BCL2 and MUM1 and negative for CD10, CD30 & cyclin D1(Fig 2 d-f). Based on the morphological and IHC features a diagnosis of low grade B cell lymphoma was given and further workup was advised for ascertaining primary vs a secondary origin. A Whole body PET scan showed hypermetabolic enlarged lymph node in axilla, neck, abdomen, and pelvis.
A cervical lymph node biopsy performed showed diffuse effacement of the nodal architecture by atypical lymphocytes with similar morphology and Immunohistochemistry profile, confirming the diagnosis as low grade B cell lymphoma of nodal origin likely Small Lymphocytic Lymphoma (SLL) with secondary cutaneous B cell Lymphoma. Patient is presently on chemotherapy with rituximab and bendamustine, completed 5 cycles and showing good response with resolving skin lesions (Fig. 1-b). This case is being reported for the rarity of its presentation and potential pitfalls in the diagnosis.

**Discussion**

Cutaneous B cell lymphomas can arise primarily from the skin or may occur due to secondary spread from nodal lymphomas \[3\]. Primary lymphomas are confined to the skin without systemic spread, and they differ from secondary lymphomas in their clinical behavior, treatment, and prognosis \[4\]. Formation of granulomas has been rarely reported in association with cutaneous lymphoma. Granulomatous changes may precede, develop simultaneously, or develop after the diagnosis of cutaneous lymphoma. The etiology of chronic granulomatous inflammation may vary ranging from infections, autoimmune disorders, toxins, allergens to neoplasms. It is characterized by aggregates of histiocytes (macrophages), which appear epithelioid, with round-to-oval nuclei and granular eosinophilic cytoplasm which frequently form multinucleated giant cells \[5\]. The pathophysiology of systemic lymphoma-associated granulomas is still unknown; although some hypotheses have been formulated, none are supported by experimental data \[6\]. Accordingly, this granulomatous reaction might represent a cytokine-mediated systemic host-response to the tumor with non-specific stimulation of the immune system including histiocytes. This could explain the possible relationship between the aggressivity of the lymphoma and the importance of the cutaneous lesions. Another hypothesis is that granulomas represent a hypersensitivity reaction against tumoral cells or viral antigens such as HTLV1 \[5, 7\]. A triggering role of chemotherapy has been proposed in some cases through the massive release of tumoral antigens.

Our patient, 72-year-old male with no prior comorbidities presented with painless erythematous papules and nodules...
over the forehead, trunk, and limbs with generalized lymphadenopathy of short duration which on work up was diagnosed low grade secondary cutaneous B cell Lymphoma. The histopathological examination of skin biopsy showed a thinned out epidermis with a diffuse, dense infiltrate of monomorphic population of lymphocytes in the dermis. The subepidermis showed a clear grenz zone with no epidermotropism, pointing towards a probable B cell Neoplasm. The lymphoid infiltrate was extending to the adnexal structures and subcutaneous fat and was composed of small to intermediate cells with a round to oval, non-cleaved, hyperchromatic nucleus. Interspersed between these cells were collections of foamy histiocytes forming granulomas along with multinucleate giant cells. The differentials considered at this stage included: B cell lymphoma, T cell lymphoma and cutaneous pseudolymphoma, with the morphology favoring a B cell lymphoma over the others. With the help of immunohistochemistry markers CD20 the lineage of the cells was established as B cell. Further IHCs including CD5, CD 23, BCL 2 confirmed the diagnosis of low grade cutaneous B cell lymphoma with a high probability of SLL. The cells were negative for CD10, CD30 & cyclin D1 excluding a mantle cell lymphoma and Hodgkin lymphoma. Similar case of DLBCL associated with chronic granulomatous inflammation was reported by Nyunt et al. in 2016. This patient was initially misdiagnosed as tuberculosis (TB) owing to the presence of chronic granulomatous inflammation on biopsy suggestive of TB. Since the patient clinical symptoms showed no improvement, another biopsy was performed which showed DLBCL. Consequently, chemotherapy was initiated and she responded well to this treatment [8].

Over years, epithelioid granulomas have been reported in associated with various malignant solid tumors and lymphomas, including Hodgkin lymphoma (HL) (more common) and various types of NHL [9]. However, there is limited knowledge and scarce data about chronic granulomatous inflammation in association with B cell lymphoma and skin lesion as the chief presenting complaints [10].

Conclusion
Skin lesion can be the only presenting symptoms in secondary cutaneous B cell lymphoma without B symptoms. A high index of suspicion for lymphoma in biopsy showing granuloma along with dense lymphoid infiltrate is thereby advised. Skin can be a "potential diagnostic clue" in the evaluation of lymphoma.

References