A Case of Cutaneous ALCL in a Patient with Sarcoidosis

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Abstract
Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin’s lymphoma (NHL) that can present with difficult-to-diagnose cutaneous symptoms. Here we present a patient with a history of cutaneous sarcoidosis who was complaining of worsening subcutaneous nodules on her lower extremities. What may have easily been misdiagnosed as recurrent sarcoidosis was biopsy-proven to be a rare case of CD30-positive large cell lymphoma. The association between sarcoidosis and malignancy has been a topic of debate for many years. Here we explore the possible correlation between sarcoidosis and lymphoma and whether our patient’s history of sarcoidosis placed her at an increased risk for developing cutaneous ALCL. We also review the two main clinical presentations of ALCL, systemic and primary cutaneous.

Introduction
Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin’s lymphoma (NHL) involving proliferation of neoplastic lymphoid cells of either T- or null-cell lineage and expressing the CD30 antigen. ALCL comprises only about 3% of all lymphomas in adults and 10% to 30% of lymphomas in children. Clinically, there are two main subtypes of ALCL: systemic (S-ALCL) and primary cutaneous (PC-ALCL). Both share the same histopathologic features, but they differ with respect to their clinical and biologic characteristics. S-ALCL is an aggressive lymphoma affecting internal organs and lymph nodes. Patients typically present with painless lymphadenopathy and systemic B symptoms such as fever, weight loss, and fatigue. Additionally, S-ALCL may secondarily involve the skin and present with cutaneous lesions, which affects 10% to 20% of S-ALCL patients.

PC-ALCL, on the other hand, is a localized and indolent lymphoma primarily affecting the skin. Extracutaneous dissemination occurs in about 10% of patients with PC-ALCL and mainly involves the regional lymph nodes. PC-ALCL lesions are typically confined to the upper extremities and most commonly occur in males. The lesions present as tender, slow-growing, solitary or localized erythematous nodules with suppurative ulcers. Multifocal lesions are seen in about 20% of patients. Due to the rarity of PC-ALCL and its clinical similarity with other cutaneous diseases, many patients with PC-ALCL go undiagnosed for years before receiving treatment.

Life expectancies and disease prognoses vastly differ between the two subtypes. PC-ALCL has a favorable prognosis, with a 10-year disease-related survival rate exceeding 85 percent. In contrast, S-ALCL is much more aggressive, with a disease-related five-year survival rate of 29% to 44%.

Case Report
A 60-year-old African American women with a history of cutaneous sarcoidosis presented with painful nodules dispersed over her lower extremities. The nodules had been present and growing in size for the past three months and were beginning to ulcerate (Figure 1). The patient admitted to discomfort and increasing pain in her legs, especially at the tumor sites, but denied any systemic symptoms of fever, chills, joint pain, or weight loss.

On physical examination, there were tender, 3-cm to 5-cm erythematous nodules with induration and secondary ulceration diffusely spread over her lower legs, as well as two to three solitary lesions on her bilateral upper forearms. A biopsy was taken from an intact nodule on the right lower leg. Histological review showed infiltrates of plump amphophilic cells, with abundant cytoplasm and irregular vesicular nuclei within the dermis (Figure 2). Immunostaining for CD30, CD3, CD20, CD117, S-100, Melan-A, CD1a, pankeratin, CK903, CK20 and CK7 was positive only for CD30, establishing a diagnosis of CD30-positive anaplastic large cell lymphoma. The patient’s clinical picture did not correspond with either PC-ALCL (typically solitary nodules, most often seen in men, with spontaneous regression) or S-ALCL (typically noted lymphadenopathy and B symptoms). Although our patient did not present with either lymphadenopathy or systemic symptoms, her multifocal presentation and the severity of her lesions were initially suggestive of systemic involvement. Furthermore, the location of her nodules, primarily on her lower extremities, was atypical and believed to be indicators of a poor prognosis.

On further work-up, the patient’s HTLV antibodies for infectious acquired lymphoma were negative, and she had no signs of systemic involvement except for leukocytosis. PET scan demonstrated multiple subcutaneous and cutaneous nodules limited to the legs and arms, representing primary cutaneous anaplastic large cell lymphoma (PC-ALCL). The patient was advised to begin chemotherapy as soon as possible.

Due to our patient’s history of sarcoidosis, her atypical presentation, and the rare nature of her neoplasm, a correct clinical diagnosis of PC-ALCL was difficult to establish. It was only once a thorough work-up was performed and a PET scan was completed that the diagnosis of PC-ALCL was established, a delay that significantly impacted the patient’s disease prognosis.

Discussion
This case shows the importance of differentiating the cutaneous lesions of ALCL from sarcoidosis and distinguishing between PC-ALCL and S-ALCL. Subcutaneous nodular sarcoidosis lesions are usually nontender, firm, flesh-colored or violaceous nodules that are 0.5 cm to 2 cm in diameter. PC-ALCL typically presents as solitary nodules, most often seen in men, with spontaneous regression, while S-ALCL typically presents with noted lymphadenopathy as well as B symptoms.

It is significant to ask whether sarcoidosis was a risk factor for the development of ALCL in our patient. The term “sarcoidosis lymphoma syndrome” was first coined by Brincker in 1986, and the idea has...
since been re-explored in several cases. Sarcoidosis lymphoma syndrome refers to the theory that there is a linear relationship between the progression of sarcoidosis and the development of lymphoma. It is believed that lymphoma and other malignancies develop more often than expected in middle-aged patients with chronic active sarcoidosis as a consequence of the chronic inflammation and immunological abnormalities initiated by sarcoidosis.\textsuperscript{16} Sarcoidosis reflects a dysregulation of the immune system due to a persistent antigenic stimulus, causing the formation of non-caseation granulomas. Persistent immune dysregulation and inflammation may lead to unbalanced proliferation of immune cells and the development of lymphoproliferative disease.\textsuperscript{16} If sarcoidosis and lymphoma occur in association, lymphoma almost invariably develops subsequent to sarcoidosis after disease-free intervals of a number of years, similar to the timeline presentation in our patient.

Brincker made the first attempt to objectively quantify the incidence of lymphoma in patients with sarcoidosis. In a 10-year study, 48 sarcoidosis patients out of 2,544 developed malignant neoplasms.\textsuperscript{15} Rømer revisited this issue in a 1998 study in which 48 of 555 sarcoidosis patients developed malignancy.\textsuperscript{17} Following those studies, a Swedish risk analysis of cancer in sarcoidosis patients not only showed that sarcoidosis and malignancy may be etiologically related in at least 25% of patients but also specified a predilection for lymphoma tumors to affect the same organs affected by sarcoidosis.\textsuperscript{18}\textsuperscript{19} This is especially interesting in the context of our patient, who was diagnosed with cutaneous lymphoma localized to her lower extremities four years after an initial diagnosis of cutaneous sarcoidosis. Although the association between sarcoidosis and malignancy has not yet been established, medical literature exploring this relationship is on the rise.\textsuperscript{20}\textsuperscript{21} To date, there have been at least five cases of patients with sarcoidosis and concurrent cutaneous T-cell lymphoma.\textsuperscript{22}\textsuperscript{23} It is our belief that a causality link between sarcoidosis and malignancy, especially lymphoma, requires greater consideration. There needs to be more meticulous care in examining and biopsying cutaneous nodules in sarcoidosis patients in order to recognize a diagnosis of cutaneous lymphoma.

**Conclusion**

Cutaneous ALCL is extremely rare and infrequently encountered in a dermatology setting. Due to the rarity of this neoplasm and its wide spectrum of clinical presentations, a proper diagnosis can be difficult to make. Familiarity with potential risk factors, such as sarcoidosis, and early manifestations are essential in making an accurate and timely diagnosis. Furthermore, distinguishing between the two subtypes, S-ALCL and PC-ALCL, is imperative in providing effective management and an accurate prognosis.

**References**


