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Anaplastic large cell lymphoma localized to the left breast years after radiotherapy for breast cancer

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Abstract

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma that can involve the skin primarily or secondarily. Our case describes an unusual presentation of eruptive tumors localized to the left breast region several years following breast cancer surgery and radiation for carcinoma of the breast. This report highlights the challenges in reaching the diagnosis of an aggressive systemic lymphoma presenting on the skin.

Keywords: non-Hodgkin lymphoma, anaplastic large cell lymphoma, ALK

Introduction

Anaplastic large cell lymphoma (ALCL) is a rare non-Hodgkin lymphoma that can be challenging to fully characterize based on clinical and pathological criteria alone [1]. As the prognosis and management differ vastly between the primary cutaneous form and its systemic counterpart with secondary cutaneous metastases, it is imperative to differentiate between these two [2]. Although histopathology and immunohistochemistry may suggest one diagnosis over the other, radiologic staging is required for definitive diagnosis [3]. This case report describes the first ALK1-negative systemic ALCL in which multiple skin lesions localized to a previously irradiated breast following breast cancer therapy. We discuss differential diagnoses and challenges in such a scenario, thereby highlighting the correct approach that should be taken.

Case Synopsis

An 85-year-old woman presented with a 3-week history of rapid onset, multiple asymptomatic papules and nodules, predominantly localized to the left breast. Her only other complaint was fatigue. Past medical history was significant for ductal carcinoma in situ of the left breast, status-post lumpectomy and adjuvant radiation 9 years prior. More recently she had been diagnosed with primary invasive ductal carcinoma of the contra-lateral breast.

Physical examination revealed multiple 0.3-2 cm erythematous to violaceous, firm papules and nodules on the left breast and adjacent left upper abdomen (**Figure 1**). Besides four papules on the right upper abdomen and back, the rest of her skin exam was unremarkable. Small, 1 cm, non-tender, mobile lymph nodes were appreciated in the pre-auricular and post-auricular regions. The clinical differential diagnoses at this point included cutaneous metastases of invasive ductal carcinoma, radiation-induced angiosarcoma of the breast, and cutaneous lymphoma.

Punch biopsy from a right abdomen nodule revealed a diffuse atypical lymphoid infiltrate involving the reticular dermis (**Figure 2**). The infiltrate was composed of medium-large lymphocytes that had irregular/convoluted nuclear contours and abundant clear to lightly eosinophilic cytoplasm. Rare multinucleated forms with wreath-like configurations and occasional mitotic figures were seen. There was no epidermotropism. The large atypical lymphocytes were CD3+, CD4+, CD8-, CD30+ (100% with diffuse staining), CD45+, CD56-, CD20-, EMA-, and ALK1-

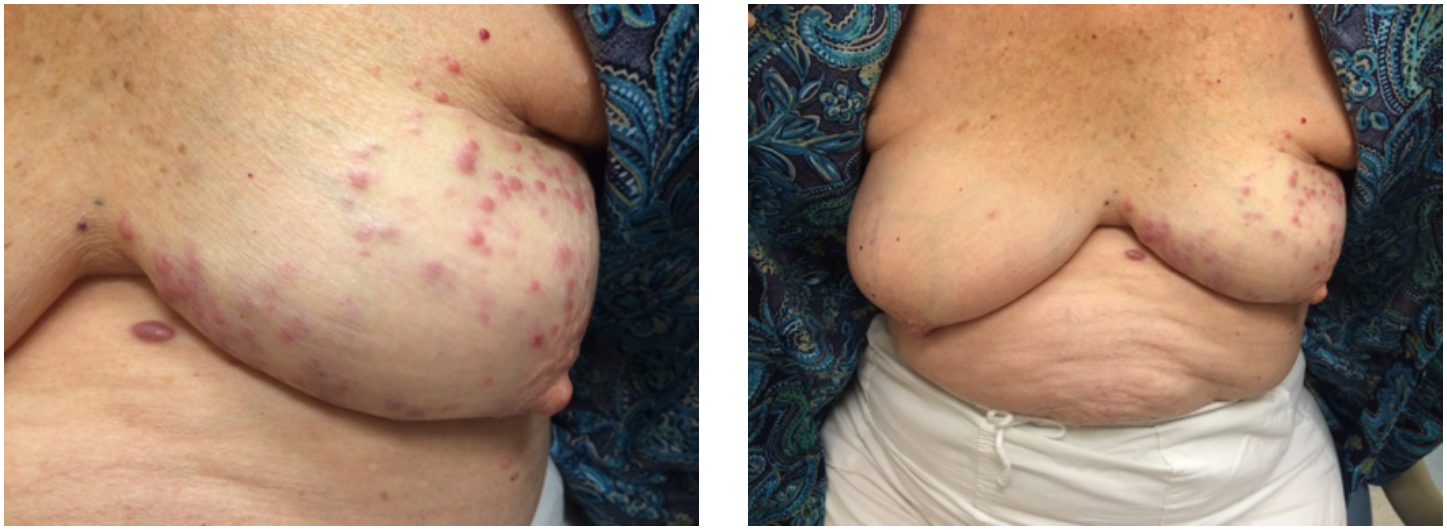

Figure 1. *The patient presented with papules and nodules predominantly localized to the left breast (left), sparing the remainder of the body from the eruption (right).*

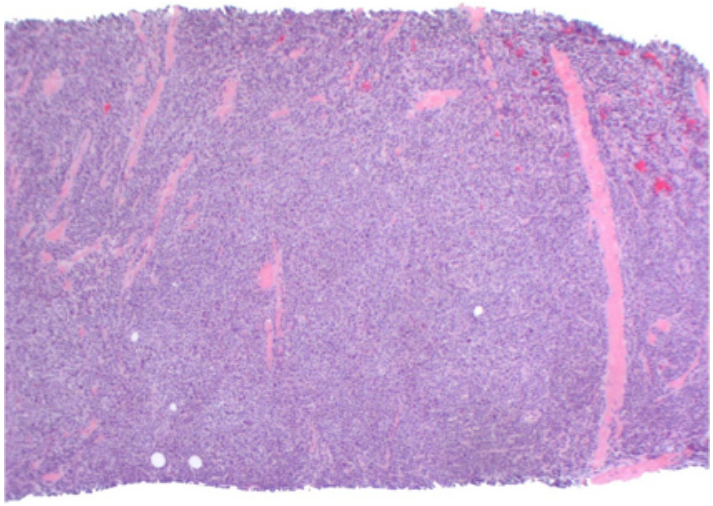

Figure 2. *Histology revealing diffuse dermal infiltrate of medium to large atypical lymphocytes. H&E, 40x*

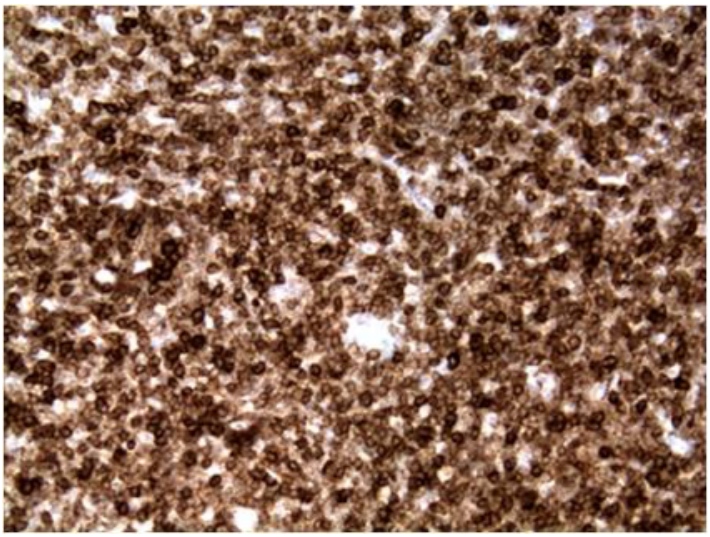

Figure 3. *CD30 stain is diffusely positive as shown, while ALK-1 stain is negative (not shown), 200x*

(**Figure 3**). The histopathology was consistent with a cutaneous CD30+ T cell lymphoproliferative disorder and clinicopathological correlation favored anaplastic large cell lymphoma (ALCL) over lymphomatoid papulosis. The histological staining patterns suggested primary cutaneous ALCL (pc-ALCL) over systemic ALCL (s-ALCL).

Laboratory values were notable for markedly elevated LDH (1850 U/L), calcium (11.2 mg/dL), creatinine (1.48 mg/dL), and uric acid (11.9 mg/dL). Complete blood count was unremarkable. Positron emission tomography scan with CT assistance (PET/CT) identified extensive disease within the liver, skeleton, lungs, subcutaneous tissues, and central nervous system.

Based on these results, the patient was diagnosed with s-ALCL with secondary cutaneous metastases. She was treated with brentuximab vedotin 1.8 mg/m2 but subsequently developed massive tumor lysis syndrome. Unfortunately, she deteriorated rapidly after developing multi-organ failure and succumbed one week later.

Case Discussion

Anaplastic large cell lymphoma (ALCL) is a rare non-Hodgkin lymphoma characterized by large diffusely CD30+ anaplastic cells with T- or null-cell lineage. The World Health Organization classification

differentiates pc-ALCL, which is limited to the skin at the time of presentation, from its systemic counterpart, s-ALCL [1]. Systemic-ALCL is further categorized into the more common ALK1-positive and the rarer ALK1-negative subtypes [4]. ALK1 (anaplastic lymphoma kinase) is a chimeric fusion protein formed by the juxtaposition of a translocated ALK gene (chromosome 2p23) with a nucleophosmin gene (chromosome 5q35), [5]. ALK1-positive s-ALCL is commonly associated with younger populations and a more favorable prognosis (5-year survival 70-80%) [2], whereas ALK1-negative s-ALCL typically occurs in older populations and has a worse prognosis (5-year survival 50%), [2, 4, 5].

Primary cutaneous-ALCL presents clinically as a rapidly growing solitary tumor or multiple grouped nodules, as seen in our patient. Histologically, pc-ALCL can be indistinguishable from s-ALCL with secondary skin metastasis. Differentiating between the two is key, however, as pc-ALCL has an indolent behavior with excellent prognosis compared to s-ALCL [2]. Ancillary studies may be helpful in distinguishing the two histopathologically. The vast majority of ALK-positive s-ALCL are positive for epithelial membrane antigen (EMA), which is absent or only focally expressed in pc-ALCL. However, ALK-negative s-ALCL may be negative for EMA. Expression of cutaneous lymphoma antigen (CLA) favors a diagnosis of pc-ALCL, though rare cases of CLA+ s-ALCL have been reported [6]. Primary cutaneous-ALCL is classically ALK-negative, but recent reports have identified rare cases contrary to this. Therefore, there is no specific histologic or phenotypic marker that can reliably distinguish pc-ALCL from its systemic counterpart; definitive distinction should always be confirmed with PET/CT [3].

Regarding therapy, surgical excision or local radiotherapy are typically first-line therapy for localized pc-ALCL with excellent outcome. In cases of multi-focal pc-ALCL, low-dose methotrexate or systemic retinoids such as bexarotene are preferred [7]. CHOP (cyclophosphamide, hydroxydaunomycin [doxorubicin], oncovin [vincristine], prednisone) is the standard chemotherapy for s-ALCL with favorable results in ALK1-positive s-ALCL, albeit less impressive results in ALK1-negative s-ALCL. When CHOP is ineffective, treatment escalation and allogeneic hematopoetic stem cell transplantation are often required. Another FDA-approved therapy in s-ALCL includes brentuximab vedotin, an anti-CD30 antibody drug conjugate [4]. Phase II trials of brentuximab vedotin have also demonstrated excellent responses in pc-ALCL [8].

Another clinical entity of ALK1-negative ALCL of the breast has been increasingly reported in the literature, in which there is a proposed relationship of the lymphoma with breast implants, the leading cosmetic surgical procedure performed in the United States. A recent study identified that implant-associated breast ALCL are twice as likely to be ALK1-negative compared to non-implant-associated breast ALCL. Of reported cases, initial presentations are most often implant-related with symptoms such as breast mass, tenderness, seroma, capsular contracture, and skin ulceration. Systemic involvement is uncommon, though reported [9]. Again, it is important to rule-out systemic disease with radiologic imaging given the differences in management and prognosis. Although our patient did not have breast implants, this procedure is commonly undertaken by many breast cancer patients, and ALK1-negative ALCL should be considered in the differential diagnosis if cutaneous changes are identified.

The presented case is particularly unusual given that the cutaneous lesions were almost exclusively confined to the left breast and adjacent abdomen. We hypothesize that the patient's prior radiotherapy to these areas caused local immune suppression promoting cutaneous metastases to localize to this region. This phenomenon of radiation induced immune suppression has been postulated in epidermodysplasia verruciformis patients who have developed squamous cell carcinomas in previously irradiated sites [10].

Conclusion

We describe the first case report of ALK1-negative systemic ALCL presenting as multiple skin tumors localized to a previously irradiated region for breast-cancer therapy. Our case highlights the limitations of relying on clinical presentation and histologic analysis alone in differentiating pc-ALCL from s-ALCL and underscores the importance of radiologic staging in making a definitive diagnosis.

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