A Rare Case of Erythroderma in a Primary Cutaneous Anaplastic Large Cell Lymphoma: A Diagnostic Challenge

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Abstract: Anaplastic large cell lymphoma (ALCL) is a rare form of non-Hodgkin's lymphoma. It usually originates in lymph nodes, although its origin in other tissues, including skin, has been reported. Identification of the lymphoid activation antigen (CD30) has now clearly established the lymphoid origin of ALCL. Recent reports suggest that in some cases cutaneous ALCL pre-existing skin disease may be a feature. This is usually mycosis fungoides (MF), although psoriasis has also been reported. A diagnosis of ALCL is usually made by a dermatologist following a series of diagnostic tests and procedures, including physical examination and history, blood tests, skin biopsy and/or lymph node biopsy , immunophenotyping may also be done to identify specific types of lymphoma. In selected cases, molecular tests may be helpful in establishing the diagnosis. A fifty one years old man came with chief complaint of reddish, pruritic patch all over his body and nodules on his right axilla and buttock. Two skin biopsies were collected, resulted a spongiotic psoriasiform hyperplasia found in drug eruption and mixed cellularity Hodgkin lymphoma. Immunohistochemistry (IHC) shows positive CD30 and CD43, Ki-67 on 80% of the cells and negative CD3, CD20, ALK, CD1a, CD15, PAX-5, AE1/AE3 with conclusion of non-Hodgkin lymphoma - ALCL.

1 INTRODUCTION

Erythroderma is defined as a generalized redness and scaling of the skin. However, it does not represent a defined entity, as it is the clinical presentation of a variety of diseases. Most commonly, erythroderma is due to generalization of pre-existing dermatoses (such as psoriasis or atopic dermatitis), drug reactions or cutaneous T-cell lymphoma (CTCL). Attention should also be focused on the potential systemic complications of erythroderma including death. In addition, long-lasting erythrodermas may be accompanied by cachexia, diffuse alopecia, palmoplantar keratoderma, nail dystrophy and ectropion (Bolognia et al., 2012; Dento et al., 1992).

Primary cutaneous $CD30^+$ lymphoproliferative disorders (PCLPD) are the second most common group of CTCL, accounting for approximately 30% of CTCLs after MF/Sézary syndrome (SS). This group includes primary cutaneous anaplastic large cell lymphoma (C-ALCL), lymphomatoid papulosis (LyP), and borderline cases (Stein et al., 2000).$CD30^+$ ALCL itself is a rare form of non-Hodgkin lymphoma (NHL), accounts for 2-3% of all NHLs and 10.2% of all T/NK-cell lymphomas (Willemze et al., 2005; Foss, 2013). ALCL may be classified according to the location of the original tumor: primary nodal, primary cutaneous, and secondary cutaneous. Primary nodal ALCL describes disease arising in lymph nodes. It typically occurs in children, runs an aggresive course, and may spread to extranodal sites, including the skin, lung, bone, and gastrointestinal tract. Primary C-ALCL originates in the skin. In contrast to primary nodal disease, it is most common in adults and is indolent. It comprises one or more tumor nodules exceeding 2 cm in diameter. Tumor nodules are often purplish red and frequently become ulcerated. Most common sites are trunk and extremities. Secondary cutaneous ALCL arises in patients with underlying CTCL, and like primary nodal disease is aggresive and carries a poor prognosis. The cutaneous lesions of all types of ALCL typically present as solitary or multiple

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ulcerated nodules, and sometimes progressed to erythoderma. Primary C-ALCL is classified as malignant tumor, normally affects adults. The majority of primary C-ALCL cases published in the literature do not show spontaneous regression (Stein et al., 2000; Willemze et al., 2005; Foss, 2013). There are two types of ALCL, ALK (anaplastic lymphoma kinase)-positive ALCL and ALK-negative ALCL. ALK-negative ALCL is a mature T-cell lymphoma with CD30 expression, morphologically identical to ALK-positive ALCL but lacks the expression of ALK. It represents 40-50% of all ALCLs, but occurs in older population (male predominance, median age 58 years) (Foss et al., 2013). In ALK-negative cases, one study showed the frequencies of the T-cell antigen expression were CD2 (100%), CD3 (50%), CD4 (40%), CD7 (40%), CD5 (25%), and CD8 (20%) (Muzzafar et al., 2009). Other study noted the expression of CD15 is aberrant, and a negative CD20 and PAX-5 (both are rarely positive in ALCL) indicated a NHL (Pletneva & Smith, 2014).

The affected individuals present with lymphadenopathy, and extranodal involvement is very rare. Because C-ALCL and systemic forms are morphologically and immunophenotypically identical (and C-ALCL cen extend locoregionally to lymph nodes), the clinical information is imperative to distinguish between the two (Stein et al,. 2000). When skin lesions are presenting manifestation of systemic ALCL (S-ALCL), the distinction of skin lesions in S-ALCL from $CD30^+$ PCLPD is imperative. The distinctions between these two can be difficult on purely clinical grounds and may be difficult as well to achieve by routine histopathology. ALK protein is expressed in skin lesions of most patients with S-ALCL but not in the large majority of patients with $CD30^+$ PCLPD (Foss et al., 2013).

The cytology of the tumor cells is identical to ALK-positive ALCL but, in general, the tumor cells tend to be larger and pleomorphic than its ALK-positive counterpart. Histologic variants are not strictly defined, but some cases resemble the lymphohistiocytic variant and others the Hodgkin-like forms. The background cells can include histiocytes, plasma cells, eosinophils, and small lymphocytes (Stein et al., 2000). Tumor cells in both LyP and C-ALCL are derived from activated T-cells which express CD30 antigen. The $CD30^+$ cells are larger than normal lymphocytes and have basophilic cytoplasm and large nuclei with a prominent nucleolus resembling immunoblasts. These cells often are bi- or multinucleated giving the appearance of Reed-Sternberg cells. Mitoses are frequent and often atypical. In C-ALCL, tumor cells form large clusters or sheets that generally extend from the dermal-epidermal junction down into the subcutaneous fatty tissue (Foss, 2013).

Although there is accumulating evidence that ALCL and Hodgkin disease (HD) are biologically distinct, the morphologic and immunophenotypic border between these disease categories is not sharp in all instances. These ambiguous cases contain relatively dense nodules or sheets of tumor cells with features of classic Hodgkin and Reed-Sternberg cells. One of the most difficult differential diagnoses of primary cutaneous ALCL is large cell transformation of MF which carries a worse prognosis. The large MF cells occur in sheets and are usually $CD30^+$, both features shared with C-ALCL. The diagnosis of large cell transformation of MF is generally made clinically when there are accompanying patches and plaques typical of MF. MF tumors with large cell transformation often contain a spectrum of lymphocytes with convoluted nuclei generally lacking in primary cutaneous ALCL (Foss, 2013; Muzzafar et al., 2009). ALK-positive ALCL usually has a better prognosis (5-year survival of 70%) compared with ALK-negative ALCL (5-year survival of 49%) (Foss, 2013; Pletneva et al., 2014).

2 CASE

A 51-year-old man admitted to our outpatient clinic with chief complaint of reddish and pruritic, scaly patch throughout his body which he started to recognize initially on both thighs three years ago without hospital admission. Having no improvement with herbal medicine (mangosteen extract) for about two years, and widespread of the patch, he went to the local hospital later on. He was diagnosed as psoriasis, and the dermatologist gave him moisturizer and cetirizine but still no improvement. He was then referred to Cipto Mangunkusumo National Hospital because two nodules appeared on right buttock and armpit, with the latter accompanied with purulent wound. From physical examination (Figure 1), a scaly erythematous patch spread all over his body along with alopecia of the scalp, eyebrows, and eyelashes. Fissures of the palms and soles, ectropion from both eyes, were also found. On his right axilla, a single tumor-presenting nodule covered with granulated, purulent, and necrotic tissue. The tumor was tender, ouval with 5 cm in diameter. The other one on his right buttock was 4 cm in diameter and no pain on palpation.

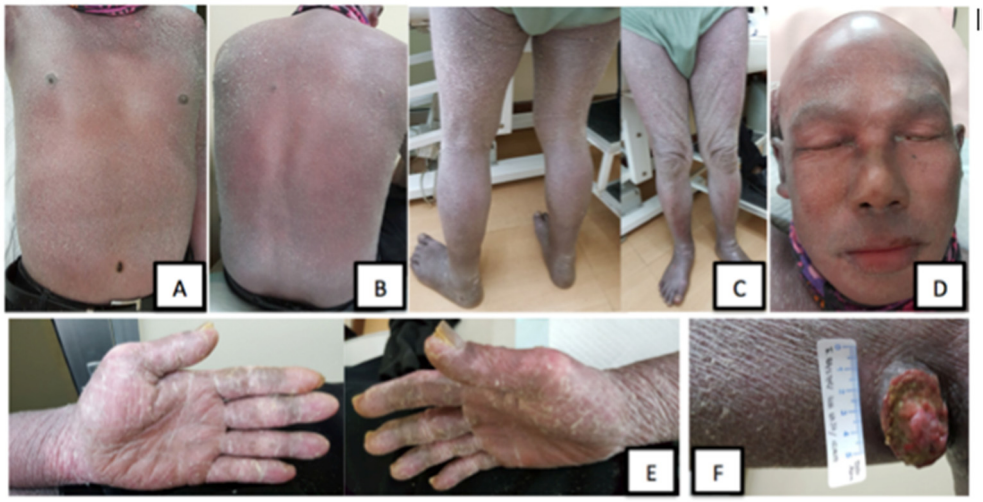

Figure 1. Patient clinically presenting with generalized erythroderma (A, B, C). Hair, eyebrows, eyelashes, mustache loss and ectropion are also seen (D). Fissures on both palms (E). A tumor-presenting ulcerated nodule on right axilla (F)

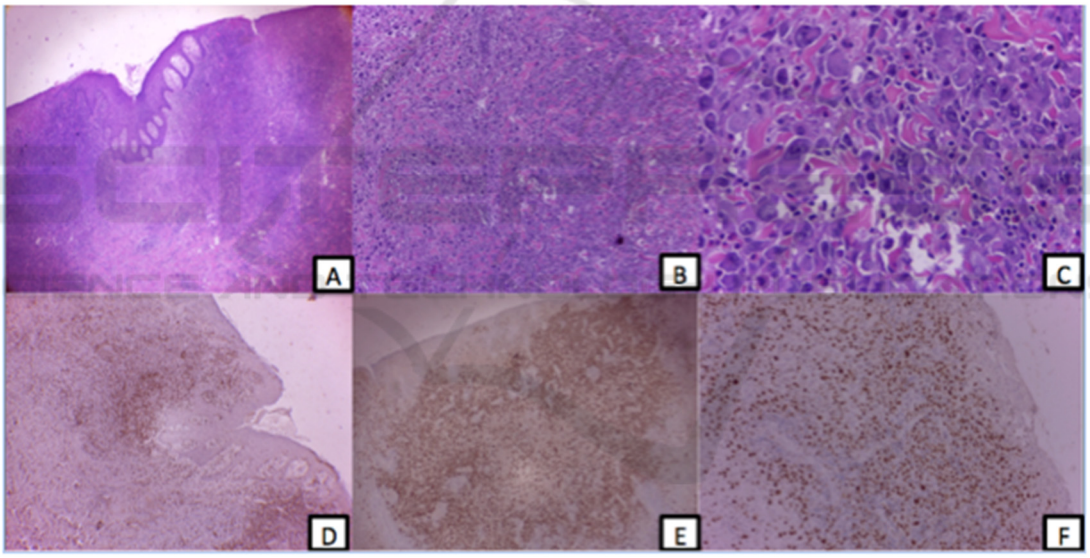

Figure 2. (A) Skin biopsy showing infiltrate with large Hodgkin-like cells in a background of small lymphocytes. (B) Lymph node from the same patient, showing thick bands of fibrosis mimicking classical Hodgkin lymphoma. (C) Section of the right axilla lymph node showed mixed cellularity Hodgkin's disease. There was effacement of the normal architecture by a mixed infiltrate comprising mononuclear Hodgkin's and bi-nuclear Reed-Sternberg cells, lymphocytes, plasma cells, eosinophils and histiocytes. In some uninvolved lymphoid tissue, a marked histiocytic response was noted. Immunohistochemistry assay shows: (D) diffuse CD3 in dermis, (E) CD30 highlights the tumor cells forming nodular aggregates divided by dense fibrosis and variability in cell size of the tumor cells, (F) a more scattered image of CD20

The patient was diagnosed as erythroderma et causa CTCL and tumor stage mycosis fungoides with secondary infection, while waiting for the confirmation from histologic findings and immunohistochemistry assay. Ultrasonography test was perfomed, with multiple lymphadenopathy were found on both inguinal and axilla, confirming systemic involvement, no intraabdominal involvement, and a cystic mass at right gluteus. The skin biopsies from two areas showed a spectrum of drug eruption from erythrodermic area of upper right arm, while the one from right axilla tumor showed mixed cellularity Hodgkin's lymphoma. The immunohistochemistry assay from right axilla tumor

resulted the following: positive CD30, CD43, Ki-67 on 80% of the atypical cells, and negative CD20, CD3, ALK, CD1a, CD15, PAX-5, and AE1/AE3 (Figure 2). These findings came to a conclusion of non-Hodgkin lymphoma, ALK-negative ALCL.

3 DISCUSSION

Anaplastic large cell lymphoma is an uncommon disease which comprises a number of heteregenous conditions. The disease usually arises in lymph nodes where these tumors morphologically resemble histiocytic lymphoma. Lymphonodal ALCL is an aggresive lymphoma with rapid extranodal spread and poor prognosis and skin involvement estimated occurs in 15% of cases. The clinical spectrum of primary C-ALCL includes plaques, nodules, and ulcerated tumours and inflammatory lesions.

The patient reported here had an unusual clinical course with a 1-year prodrome of non-specific erythroderma preceded by reddish, pruritic scaly patch on both thighs two years before. Most cases of primary C-ALCL arise in normal skin, though pre-existing mycosis fungoides is well recognized. At first we diagnosed the patient with MF because florid erythroderma with marked ectropion clinically suggestive of MF/SS, however, we still underwent further investigations for confirmation of diagnosis since a painful, ulcerated nodule appeared on his right axilla.

Two biopsies were performed during the course of the erythrodermic phase of the illness. The one from the right arm showed a hyperkeratotic epidermis, half parakeratotic, spongiotic psoriasiform hyperplasia, exocytosis of lymphocytes, and basal cells vacuolisation. Lymphoid inflammatory cells were accumulated at dermal papila. At superficial part of the dermis there were sparse infiltrate of lymphocytes. These features concluded as a drug eruption. Histological examination from the right axilla nodule showed infiltration of the dermis by atypical cells which were arranged in strands and sheets, rough chromatin, noted pleomorphic, and eosinophilic cytoplasm. Epidermis part were hyperkeratotic, parakeratotic, achantotic with granulated tissue. Reed-Sternberg cells were also found. Mitotic cells easily found. These concluded as a mixed cellularity Hodgkin lymphoma. We cannot concluded drug eruption as the diagnosis since it did not match with the patient's history and clinical features. A result of Hodgkin lymphoma was sometimes deceiving as it could also mimicking non-Hodgkin lymphoma. Thus an immunohistochemistry assay is needed to confirm the diagnosis.

Immunohistochemistry assay of this patient showed positive findings of CD30, CD43, and Ki-67 at about 80% of the anaplastic cells. CD20, CD3, ALK, CD1a, CD15, PAX-5, AE1/AE3 were negative. A positive CD30 and negative ALK strongly suggest that this patient suffer from ALCL, ALK-negative type. Based on one study, the frequency of CD3 in ALK-negative ALCL was 50%. Another study showed expression of CD15 is aberrant, and a negative CD20 and PAX-5 indicated a NHL. Thus we concluded this patient is still well-accepted in an ALCL ALK-negative spectrum, regarding negative results of CD3, CD20, and PAX-5.

4 CONCLUSIONS

We report a very rare case of erythroderma originated from C-ALCL. It is very challenging for us to establish a diagnosis regarding confusing relation of history, clinical, histopathologic, and immunohistochemistry findings of the disease, including a Hodgkin disease-mimicking feature of NHL and various immunohistochemistry assay results. ALCL itself is already a rare case in a population and an erythroderma with a painful, ulcerated nodule make it more laborious for dermatologists and pathologists to establish a diagnosis. This unusual case both expands the spectrum of cutaneous disease associated with erythrodermic ALCL and highlight the importance of early biopsy and immunochemistry in patients with erythroderma presentation.

REFERENCES

Bolognia, JL., Jorizzo, JL., Schaffer, JV., 2012. Dermatology. 3rd ed. China: Elsevier. Chapter 10, Erythroderma; p. 171-82

Denton, K., Wilson, C. L., & Venning, V. A., 1992. Primary cutaneous anaplastic large-cell lymphoma with a prolonged erythrodermic prodrome. *British Journal of Dermatology*, *126*(3), pp. 297-300.

Foss, F., 2013. *T-cell lymphomas.* New York: Humana Press. Chapter 2. Epidemiology and prognosis of T-cell lymphoma; p. 25-40.

Foss, F., 2013. *T-cell lymphomas.* New York: Humana Press. Chapter 5. Primary cutaneous and systemic $CD30^+$ T-cell lymphoproliferative disorders; p. 71-86.

Muzzafar, T., Wei, E. X., Lin, P., Medeiros, L. J., & Jorgensen, J. L., 2009. Flow cytometric immunophenotyping of anaplastic large cell lymphoma. *Archives of pathology & laboratory medicine*, *133*(1), pp. 49-56.

Pletneva, M. A., & Smith, L. B., 2014. Anaplastic large cell lymphoma: features presenting diagnostic

challenges. *Archives of Pathology and Laboratory Medicine*, *138*(10),pp. 1290-1294.

Stein, H., Foss, H. D., Dürkop, H., Marafioti, T., Delsol, G., Pulford, K., ... & Falini, B., 2000. CD30+ anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood*, *96*(12), pp. 3681-3695.

Willemze, R., Jaffe, E. S., Burg, G., Cerroni, L., Berti, E., Swerdlow, S. H., ... & Grange, F., 2005. WHO-EORTC classification for cutaneous lymphomas. *Blood*, *105*(10), pp. 3768-3785.