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CD30+ Anaplastic large cell lymphoma with bullous lesions: Good results with steroid + cyclosporine treatment

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Abstract

Anaplastic large cell lymphomas (ALCLs) are type of lymphomas with a strong CD30 positivity. A 38 year old lady presented with tender nodules over forearms and thighs, blisters and ulcerations over forearms, swelling of parotids and induration over forearms, flanks and left breast. MRI showed subcutaneous oedema of anterior abdominal wall, oedema of left breast extending into the parenchyma, hepatosplenomegaly. Histopathology revealed rimming of fat cells by atypical lymphoid cells, immunohistochemistry studies revealed CD30, CD3, CD4, CD5 positivity. T cell receptor gamma chain gene rearrangement (TCR) assay showed an oligoclonal population of T cells. The patient was started on parenteral steroids and oral cyclosporine. The bullae and ulcers healed, the induration score dropped from 15 to 0 in 21 days. The drugs were gradually tapered to a maintenance dose. There was complete remission with cyclosporine and steroids with no evidence of relapse after 16 months. Hence cyclosporine and steroids can be used either singly or in combination depending on the severity, dissemination and response.

Keywords: Cyclosporine, ALCL, CD30, HPS.

Introduction

Anaplastic large cell lymphoma (ALCL) includes a group of large cell lymphomas with a strong CD30 positivity. Two pathologically distinct entities are defined, systemic ALCL and primary cutaneous ALCL (PC-ALCL). According to 2008 WHO classification, PC-ALCL is a part of primary cutaneous CD30 $^{+}$ T-cell lymphoproliferative disorder.(1) PC-ALCL and systemic ALCL share a common feature which is CD30 positivity but the former lacks expression of anaplastic lymphoma kinase (ALK) protein.(2) PC-ALCL is demonstrated in 9% of cutaneous lymphomas and is commonly seen in elderly.(3) Clinically presents as erythematous nodules and ulceration on head and extremities. PC-ALCL has an excellent prognosis. When the lesions are multifocal low-dose MTX, retinoid or IFN alpha is recommended.(4) There is a paucity of studies in the use of cyclosporine for the treatment of ALCL, in our case the patient has shown good clinical response on treatment with cyclosporine. We report a case of ALK negative CD30 positive PC-ALCL with bullous lesions, histopathologically showing SPTCL like pattern who responded well to a combination of cyclosporine and steroids; attained complete remission with no evidence of clinical relapse after 16 months of follow-up.

Case Report

A 34 year old lady presented with painful reddish lesions over the body, blisters over the forearms, high grade fever since two months. She was pale and icteric with no significant lymphadenopathy. There was pitting edema of hands. Cutaneous examination revealed tender, firm, erythematous nodules over medial aspect of arms; multiple flaccid bullae and ulcers with thick yellowish discharge over forearms (Fig. 1a, 1b).

There was induration over forearms, parotid region, left breast extending vertically from upper outer quadrant to 10cm below the areola and horizontally upto anterior axillary line with lower quadrant showing peau d' orange appearance (Fig. 1c). Skin over flanks, epigastric and suprapubic region was indurated. Mucosae were normal. Seven years back she presented to the same hospital with erythematous nodules and fever. Histopathological examination revealed rimming of fat cells by atypical lymphoid cells and Immunohistochemistry showed positivity for CD3 and CD5. However the patient was lost for follow up before initiation of treatment. On enquiring, she revealed history of taking various medications from several centers details of which were not available. We considered the following differential diagnosis; Subcutaneous panniculitis like T-cell lymphoma (SPTCL), ALCL, bullous pemphigoid, erythema nodosum and lupus panniculitis.

Investigations revealed evidence of severe anemia (Hb-7.5g%), thrombocytopenia (platelet count-48000/microliter), altered liver functions (total bilirubin-3.6mg/dl, direct bilirubin-1.58mg/dl, SGOT/SGPT-290/98U/l, ALP-1495U/l), elevated triglycerides (TG-246mg/dl) and serum ferritin (418ng/ml). There was no pulmonary involvement and renal functions were within normal limits. MRI abdomen showed hepatosplenomegaly, cholelithiaisis and subcutaneous oedema in the anterior abdomen (Fig. 2a). MRI breast showed mass lesion in the left breast with infiltration into the overlying skin (Fig. 2b).

Skin biopsy from the nodule and ulcer over the right forearm and arm showed thinned out epidermis. Superficial dermis showed mild edema, dilated blood vessels and infiltration by lymphocytes a few of which showed large convoluted nuclei, subcutaneous tissue showing lobular infiltration by atypical lymphocytes, beading of fat cells by atypical lymphoid cells, few neutrophils and plenty of apoptotic bodies suggestive of SPTCL with no evidence of hemophagocytosis (Fig. 3a). Biopsy from the bulla showed a subepidermal split with lymphomatous infiltrate (Fig. 3b). Direct immunofluorescence studies were not done. Immunohistochemistry was positive for CD30 (Fig. 3c), CD3 (Fig. 3d), CD4, CD5 and was negative for CD 20, CD 56, CD8, EMA, ALK-1.

Epstein-Barr virus encoded early RNA expression (EBER) was negative.

TCR gamma chain gene rearrangement was inconclusive showing oligoclonal population of T-cells. Bone marrow aspiration revealed hypercellular marrow with erythroid and megakaryocytic hyperplasia, however bone marrow biopsy did not show evidence of malignancy. Fine needle aspiration cytology (FNAC) and a skin biopsy were done from the left breast lesion, they did not show any features suggestive of ALCL. FNAC of the parotid gland showed evidence of sialadenitis. Based on histopathology and immunohistochemistry studies we made a final diagnosis of PC-ALCL histologically mimicking SPTCL.

Induration in our case was assessed once in three days based on a score (0-no induration; 1-mild induration; 2-moderate induration; 3-severe induration). To overcome the interobserver variation, a single observer assessed the induration throughout the treatment period. The total score was 15 on day 0.

She was started on parenteral antibiotics and steroids equivalent to prednisolone 80mg/day and oral cyclosporine 3.5mg/kg body weight (100mg twice daily). She was transfused with two units of packed red blood cells. The bullae and ulcers healed (Fig. 1d), the induration score dropped from 15 to 0 in 21 days (Table 1).

A subjective assessment based on a scale of 0-10 dropped to 0 in 15 days. Liver functions, serum ferritin, triglyceride levels were normal by the end of 2 months. Parenteral steroids were converted to oral steroids. Cyclosporine and steroids were gradually tapered, currently the patient is off treatment. At the end of 16 months there was no evidence of clinical relapse.

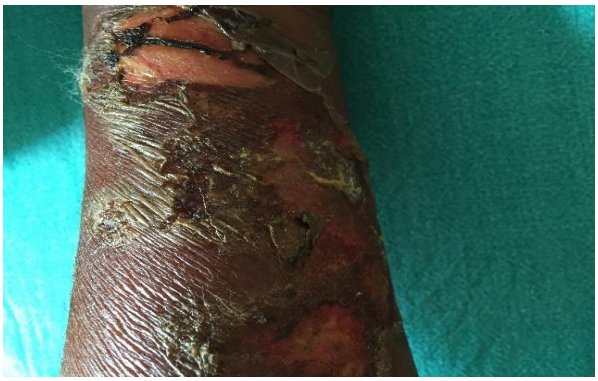

Fig. 1: Clinical photographs
1A: Flaccid ruptured bullae and ulcers over the left forearm

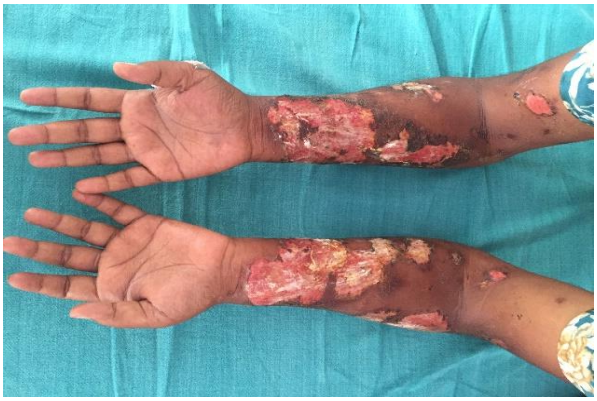

Fig. 1: Clinical photographs
1B: Erythematous nodules, ulcers with thick yellowish discharge over arms and forearms

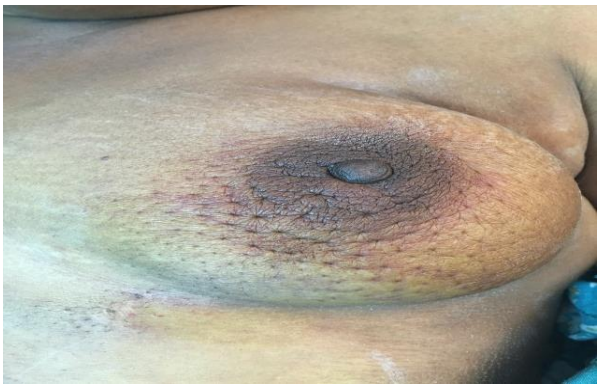

Fig. 1: Clinical photographs
1C: Left breast showing peau d' orange appearance in the lower quadrant

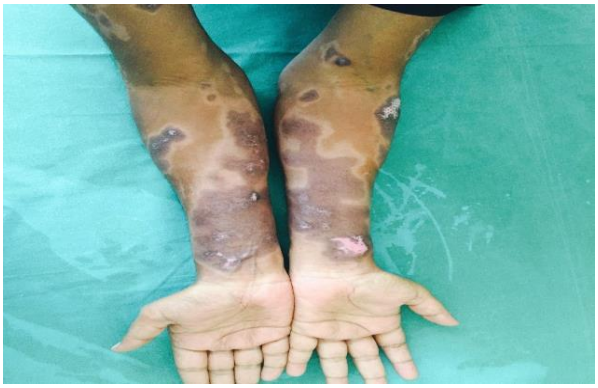

Fig. 1: Clinical photographs
1D: Complete resolution of blisters and ulcers after 21 days of treatment with steroids and cyclosporine

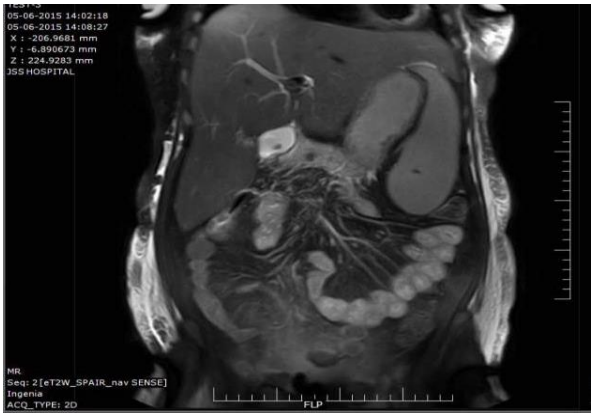

Fig. 2: MRI of the abdomen and left breast
2A: T2FS sequence of the abdomen in coronal plane shows hepatomegaly, cholelithiasis and oedema of the skin. The left breast in field of vision demonstrates the existing mass lesion

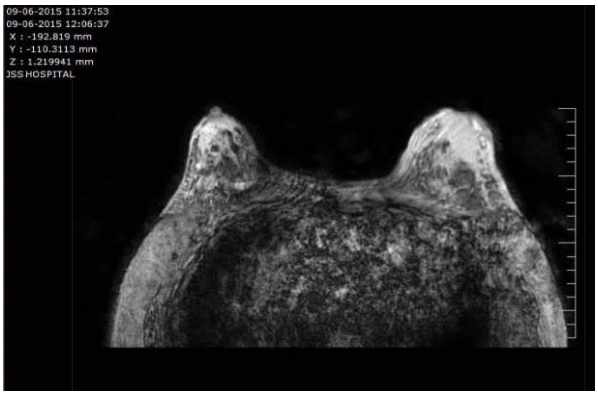

Fig. 2: MRI of the abdomen and left breast
2B: T2WI axial breast imaging demonstrating heterogenous, hyperintense, irregular mass lesion within the left breast parenchyma infiltrating the overlying skin

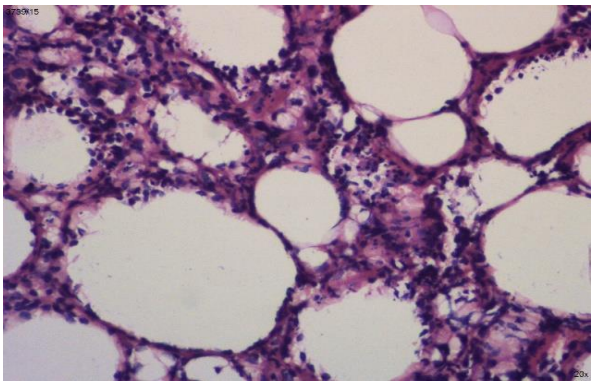

Fig. 3: Histopathology and immunohistochemistry
3A: Microphotograph showing lobular infiltration by atypical lymphoid cells with large pleomorphic hyperchromatic nuclei (H and E, x200)

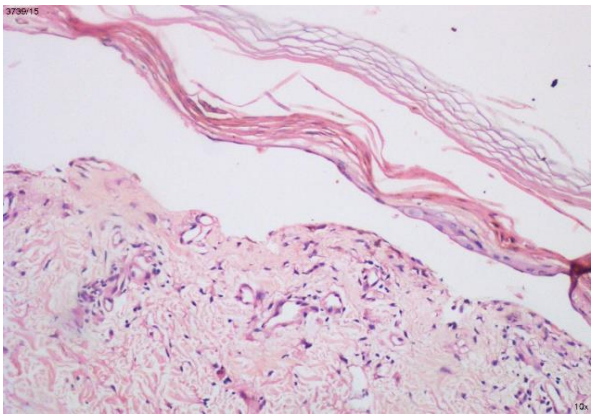

Fig. 3: Histopathology and immunohistochemistry
3B: Microphotograph showing subepidermal bulla with scattered atypical lymphoid cells in the superficial dermis (H and E, x100)

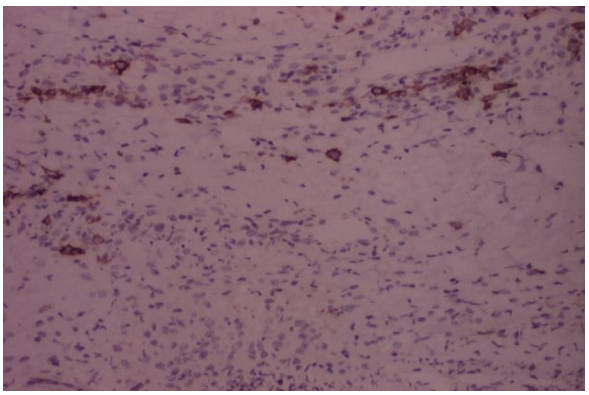

Fig. 3: Histopathology and immunohistochemistry
3C: CD30 positivity, score 3+ in atypical lymphoid cells

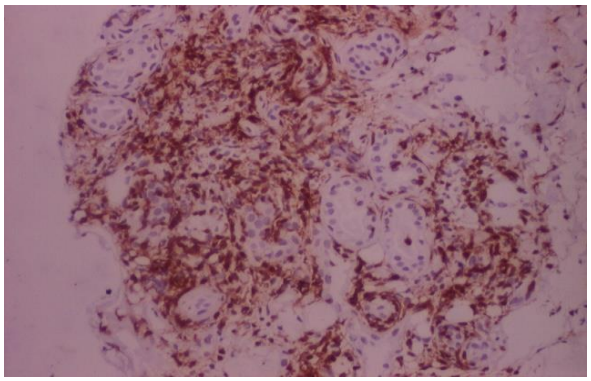

Fig. 3: Histopathology and immunohistochemistry
3D: CD3 positivity, score 4+ in atypical lymphoid cells

Table 1: Objective and subjective assessment of induration

Objective assessment (0-3)							Subjective assessment (0-10)
Days	**Right forearm**	**Left forearm**	**Right flank**	**Left flank**	**Left breast**	**Total score**	
0	3	3	3	3	3	15	10
3	3	3	3	3	3	15	10
6	1	2	2	2	3	10	7
9	0	1	2	2	2	7	5
12	0	0	2	2	1	5	3
15	0	0	1	1	1	3	0
18	0	0	1	1	1	3	0
21	0	0	0	0	0	0	0

0-no induration; 1-mild induration; 2-moderate induration; 3-severe induration

Discussion

ALCLs are type of peripheral T-cell lymphomas with a strong CD30 expression. According to 2008 WHO classification ALCL are of two types, systemic ALCL and primary cutaneous ALCL (PC-ALCL). PC-ALCL and lymphomatoid papulosis are a part of primary cutaneous CD30 $^{+}$ T-cell lymphoproliferative disorder.[1]

PC-ALCL presents with a solitary or grouped nodules, plaques, ulcers and rarely disseminate to extracutaneous sites.[4] Bullous lesions as seen in our case has been reported in a child with systemic ALCL with cutaneous involvement.[5] Extracutaneous spread is reported in 13% of the patients.[6] Our patient presented with hepatosplenomegaly and cytopenias. However there was no bone marrow or nodal involvement.

ALCL cases with SPTCL like morphology have been reported in the literature.[7] Characteristic rimming of adipocytes as seen in our case can pose a diagnostic dilemma as it can also be seen in other T and B cell lymphomas.[8] In our case, on correlating histopathologic and immunohistochemistry features we made a diagnosis of PC-ALCL.

Hemophagocytosis (HPS), a complication which is diagnosed when ≥5 of the following criteria are present; clinical: fever, splenomegaly; laboratory: cytopenias, hypertriglyceridemia, hyperferritinemia, histopathological evidence of HPS, low/lacking NK-cell activity, elevated soluble sIL-2 receptor.[9] In our case five out of eight criteria of HPS namely fever, splenomegaly, cytopenias, hypertriglyceridemia, hyperferritinemia were present, however there was no histopathological evidence of HPS in skin and bone marrow.

Multiagent Chemotherapy has been regarded as the first-line therapy in multifocal PC-ALCL.[10] The common chemotherapy combination used is CHOP (cyclophosphomide, doxorubicin, vincristine, prednisone). Methotrexate, retinoids, interferon, imiquimod thalidomide, pralatrexate are other options, for localised lesions surgical excision and radiotherapy are indicated. Chemotherapy has a remission rate of 92% with 62% having relapse and a disease-free period of 4 months in those who had a relapse.[10] PC-ALCL has an excellent prognosis with 5-year survival rates of 76-96%.[11]

As our initial histopathological diagnosis was SPTCL where cyclosporine is indicated, we started the patient on cyclosporine with steroids and the patient responded well. There was complete remission. There was no recurrence after stopping treatment and 16 months of follow-up.

Conclusion

This is a case of ALK negative CD30 positive PC-ALCL with hitherto rarely reported bullous lesions, histologically mimicking SPTCL who responded to a

combination of cyclosporine and steroids and attained complete clinical remission with no evidence of clinical relapse.

Acknowledgement

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References

1. Ralfkiaer E, Willemze R, Paulli M, Kadin ME. Primary cutaneous CD30-positive T-cell lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL et al, editors. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. France: IARC Press; 2008. p. 300–301.
2. Oschlies I, Lisfeld J, Lamant L, Nakazawa A, d' Amore ESG, Hansson U et al. ALK-positive anaplastic large cell lymphoma limited to the skin: clinical, histopathological and molecular analysis of 6 pediatric cases. A report from the ALCL99 study. Haematologica 2013;98(1):50-56.
3. Kempf W. CD30 lymphoproliferative disorders: histopathology, differential diagnosis, new variants, and simulators. J Cutan Pathol 2006;33 (suppl 1):58-70.
4. Bekkenk MW, Geelen FA, van Voorst Vader PC, Heule F, Geerts ML, van Vloten WA et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000;95(12):3653–3661.
5. Caglar K, Akyuz C, Uner A, Kutluk T, Yalçin B, Varan A et al. Anaplastic large cell lymphoma in a child presenting with cutaneous nodules and blisters. Turk J Pediatr 2005;47:188–190.
6. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol 2003;49(6):1049–1058.
7. Batrani M, Bhawan J. Pitfalls in the Diagnosis of Cutaneous Lymphoma. Am J Dermatopathol 2014;36:90-100.
8. Lozzi GP, Massone C, Citarella L, Kerl H, Cerroni L. Rimming of adipocytes by neoplastic lymphocytes: a histopathologic feature not restricted to subcutaneous T-cell lymphoma. Am J Dermatopathol 2006;28(1):9-12.
9. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S et al. Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr. Blood Cancer 2007;48(2):124–131.
10. Kempf W, Pfaltz K, Vermeer MH, Cozzio A, Ortiz-Romero PL, Bagot M et al. EORTC, ISCL and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118(15):4024–4035.
11. Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol 2009;145(12):1399–1404.