Systemic anaplastic large cell lymphoma with secondary cutaneous involvement

Sir,

A 28-year old female presented with a large swelling over the left flank for 1½ months and a painful swelling over the left groin since 15 days. Clinical examination revealed a 25 × 30 cm sized, single, firm, non-tender, erythematous, infiltrated plaque studded with reddish-brown nodules [Figure 1]. Another 8 × 10 cm firm, non-tender nodule with pustules and crusts on the surface was noted in the left inguinal region. Systemic examination was unremarkable.

Complete hemogram, peripheral blood smear, liver and renal function tests were within normal limits. Fine needle aspiration cytology (FNAC) from the inguinal region showed atypical cells and mature lymphocytes. Chest X-ray revealed hilar lymphadenopathy. CT abdomen showed multiple enlarged inguinal, pelvic, and central abdominal lymph nodes, and whole-body positron emission tomography (PET) scan revealed activity in the left inguino-femoral, pelvic, retroperitoneal and thoracic lymph nodes and diffuse splenic involvement.

Biopsy from the cutaneous mass revealed a diffuse dermal infiltrate [Figure 2a] comprising of sheets of large atypical pleomorphic lymphocytes [Figure 2b] with hyperchromatism [Figure 2c]. Epidermotropism was absent. Biopsy of left inguinal lymph node showed a diffuse infiltrate with hyperchromatic large atypical pleomorphic cells and bizarre giant cells.Immunohistochemistry both of the inguinal lymph node and skin lesion showed CD3 positivity in the surrounding small lymphocytes [Figure 3a] and a strong positivity for CD30 (Ki-1) [Figure 3b], leukocyte common antigen (LCA/CD45) [Figure 3c], and epithelial membrane antigen (EMA) [Figure 3d] in the large atypical lymphoid cells. Anaplastic lymphoma kinase (ALK) could not be tested due to nonavailability.[1] Based on these findings a diagnosis of CD30+ cutaneous anaplastic large cell lymphoma (ALCL) secondary to systemic anaplastic large cell lymphoma, stage IVB (T2 N3 M1) was made.

The patient was started on CHOP regimen (cyclophosphamide 800 mg/m^2, vincristine 2 mg, doxorubicin 50 mg/m^2 and prednisolone 60 mg/m^2). After six cycles, there was 75% improvement in the cutaneous lesion. With additional local radiotherapy (total dose 4500 cGy) there was a near complete resolution of the skin lesion [Figure 4]. However, there was no improvement in systemic disease as evidenced by post-chemotherapy whole-body PET scan which demonstrated fluorodeoxyglucose (FDG)-avid fresh lymph nodes in paratracheal, pre- and para-caval, pre- and para-aortic regions, and right supraclavicular region, along with pre-existing intra-abdominal lymphadenopathy and diffuse splenic involvement. The patient succumbed to esophageal compression within 1 year of diagnosis.

Anaplastic large cell lymphomas present as primary cutaneous (PC-ALCL) disease or systemic disease with secondary cutaneous involvement, both of which are distinct entities with different clinical and biological features. Primary cutaneous disease[2] presents as solitary or multiple large ulcerated nodules, predominantly on trunk, without evidence of mycoses fungoides or another type of primary cutaneous T cell lymphoma.[3] Histologically it is characterized by large tumor cells with pleomorphic cytomorphology, majority of which express CD30 (Ki-1) antigen.[1]

Primary cutaneous anaplastic large cell lymphoma has a favorable prognosis with a 5-year survival of >90% and needs to be differentiated from cutaneous disease secondary to systemic anaplastic large cell lymphoma, as the latter has a poor prognosis, with a 5-year survival of <45%.[2] However, presently there are no reliable biological markers to distinguish the two. Though ALK expression in the skin indicates systemic disease, there are some well-documented ALK+ve primary cutaneous anaplastic large cell lymphomas.[2] Conversely, ALK negativity in skin does not necessarily exclude systemic disease, as 20–60% of systemic anaplastic large cell lymphoma can be ALK–ve.[2] ALK expression correlates with young age, systemic disease, and usually good prognosis.[2]

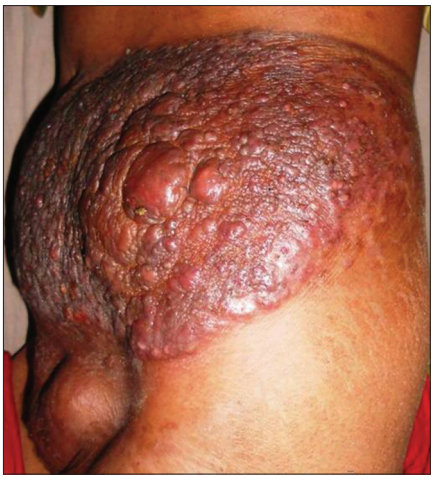

Figure 1: Erythematous, infiltrated plaque studded with many reddish-brown nodules with overlying crusting at places on the left flank

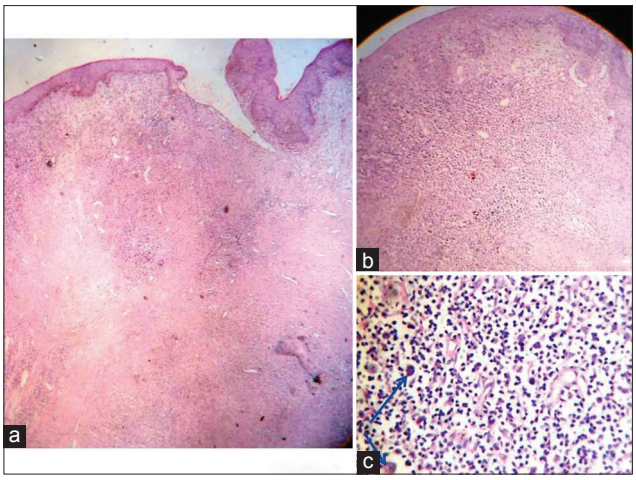

Figure 2: (a) Diffuse interstitial infiltrate involving the entire dermis (H and E, scanner view); (b) diffuse pleomorphic lymphocytic infiltrate (H and E, ×10); (c) large atypical lymphocytes with hyperchromatism (arrow) and a few eosinophils (H and E, ×40)

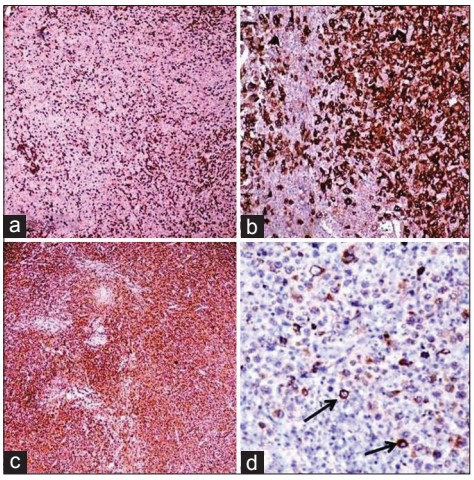

Figure 3 (a) Immunohistochemical staining profile showing CD3 positivity in surrounding small lymphocytes on lymph node biopsy; (b) diffuse CD30+ large atypical lymphocytes on lymph node biopsy; (c) diffuse cells staining positive with LCA on lymph node biopsy; (d) EMA+ ve large atypical lymphocytes (arrow) on lymph node biopsy

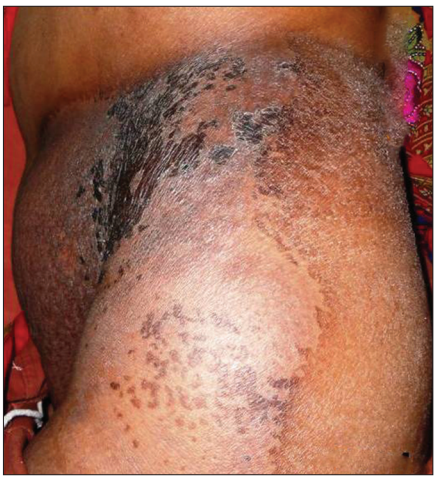

Figure 4: Almost complete regression of the skin lesions following chemotherapy and radiotherapy

About 40–65% of patients with anaplastic large cell lymphoma have extranodal disease either at the primary site or as part of the systemic process.[2] Determination of the origin of extranodal disease is critically important, particularly in the skin. EMA (MUC-1), frequently expressed in systemic anaplastic large cell lymphomas is associated with an inferior outcome in ALK−ve tumors.[3] In a study of 63 cases of systemic anaplastic large cell lymphoma, George *et al.*[3] observed that ALK+ve lymphomas more frequently (73%) expressed EMA than ALK−ve lymphomas (49%) and the 5 year survival was 70.7% for patients with EMA+ve tumors and 93.8% for patients with EMA−ve tumors.They concluded that EMA expression conferred a poorer prognosis presumably because of resistance to chemotherapy. Our patient's tumor was EMA positive, and even though her skin lesions responded to chemotherapy, her systemic disease was resistant to therapy.

Survivin, which inhibits apoptosis, is another independent prognostic marker in anaplastic large cell lymphoma. In ALK+ve tumors, when survivin is positive the 5-year survival is only 34% and when negative it increases to 100%. Similarly, in ALK–ve tumors, when survivin is positive, the 5-year survival is 46% and when negative it increases to 89%.[4]

ALK+ve patients respond better to CHOP regimen while EMA+ve patients respond poorly. The fatal outcome in our patient probably could be attributed to EMA+ve expression. Apart from chemotherapy,

anti-CD 30 monoclonal antibodies have been used to treat systemic disease. In a study by Pro *et al.*,[5] patients with relapsed/refractory anaplastic large cell lymphoma received anti-CD30 monoclonal antibody (brentuximab vedotin 1.8 mg/kg every 21 days, 16 cycles) as the second-line treatment. Tumor reduction was observed in 97% cases, while 57% achieved complete response. Our patient, a deserving candidate for this drug, could not receive it owing to its unavailability in India.

In our case, despite aggressive treatment with combination chemotherapy and local radiotherapy, the systemic lymphoma showed a negligible response. Positive EMA expression and generalized lymphadenopathy at the time of diagnosis were probable poor prognostic factors highlighting the difficulties encountered in managing aggressive disease in a resource-limited setting and the need for more promising treatment options like biologicals and immunotherapy.

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