

Anaplastic Large Cell Lymphoma of Scrotal skin

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Abstract

Cutaneous T cell lymphoma (CTCL) is an uncommon diverse group of lympho-proliferative disorders involving the skin. They vary considerably in clinical presentation, microscopic features and immunophenotyping. The diagnosis is challenging, zealous, and often not easy. CD30+ve anaplastic large cell lymphoma is extremely rare. Its clinical spectrum varies from a solitary unifocal skin lesion of excellent prognosis to a multi focal systemic disease having a poor outcome. The diagnosis is quite cumbersome, and often difficult. The differential diagnosis include from benign skin lesions to secondary cutaneous involvement by lymphoma. A correct diagnosis is integral with a complete metastatic/staging work up to avoid over treatment. The treatment options depend on extent of disease involvement and include surgical excision, surveillance, local radiotherapy, and systemic chemotherapy. The prognosis is good with unifocal local disease. We present here a very rare case of CD30+ ALCL of scrotal skin, in a middle aged male patient.

Keyword: Scrotal skin, CD30+ NHL, Unusual site NHL, Cutaneous T cell lymphoma, CD30+ ALCL, NHL, Anaplastic large cell lymphoma, Royal hospital Oman.

Introduction

Primary cutaneous CD30+ ALCL (Anaplastic Large cell Lymphoma) is a rare cutaneous T cell lymphoma (CTCL) of middle age; which includes multiple diverse subtypes depending on presentation, pathology and immunophenotype.¹ Up to 25% are reported to regress spontaneously.¹ This neoplasm can present as unifocal or multifocal (10-25%) nodules occasionally with ulceration, as an ulcer or tumour commonly on the trunk and extremities.² In 2003, first case was reported as an unusual primary cutaneous CD30+ LCL presenting initially as ulcerative papules on the hands followed by an ulcerating nodule on the scrotum.¹ There are cases reported of secondary scrotal skin involvement by lymphoma.^{4,5} Isolated involvement of scrotal skin by CD30+ ALCL is extremely rare with only a few cases reported in literature.⁴ The CD30+ LCL is also reported after burns, organ transplant, or in people on immunosuppressive therapy and can be associated with B symptoms.^{2,4} Hodgkin's Lymphoma can also involve skin but very rarely.^{1,2,5,6}

CD30+ lympho-proliferative disorders include a wide spectrum of disease with lymphomatoid papulosis at the benign end of the spectrum and cutaneous CD30+ anaplastic large-cell lymphoma (ALCL) at the malignant end.¹ Many described borderline lesions are somewhere in between. Cutaneous CD30+ (Ki-1) ALCL is clinically and pathologically heterogeneous group of lympho-proliferative disorders, leading to some difficulty in its diagnosis and subsequent classification. Expression of CD30 (an activation marker for B or T cells) in more than 75% of neoplastic cells characterizes this group of lympho-proliferative disorders.

Cutaneous CD30+ ALCL can be subdivided clinically into a primary cutaneous form without extra-cutaneous involvement, or a systemic form of disease with secondary skin involvement at initial presentation.⁶ The primary cutaneous form generally has a better prognosis than the systemic form with secondary skin involvement. Spontaneous regression of the primary cutaneous form may occur despite high-grade anaplastic cytology of neoplastic lymphocytes, in upto 25% of cases.

Cutaneous CD30+ ALCL can be further classified into different groups according to histological features and patterns (e.g., pleomorphic, immunoblastic, monomorphic, small-cell predominant, Hodgkin disease-related, and other uncommon variants); immunophenotype (e.g., T, null, B, rarely B and T); and other clinical features, such as ALCL arising in patients who are HIV positive and ALCL occurring after another lympho-proliferative process.⁷ Multiple patterns of cutaneous CD30+ ALCL are recognized, and three are recognized by the World Health Organization (common, lymphohistiocytic, and small cell); however, several others have been described in the literature, for example, neutrophil rich, subcutaneous, and inflammatory.

Case Report

A 59 year Omani male presented with complaints of lower abdominal pain, intermittent haematuria and progressive ulceration of right scrotal skin of 3 months duration. There was no associated co-morbid disease. There was a past history of Right hip surgery about 15 years back due to trauma, with no further details available. On clinical examination he was well with performance status 1 WHO, and weight 65 kg. The general physical examination was



Figure-1: Ulcerated neoplasm showing skin in the adjacent area (H & E stain x 10X).

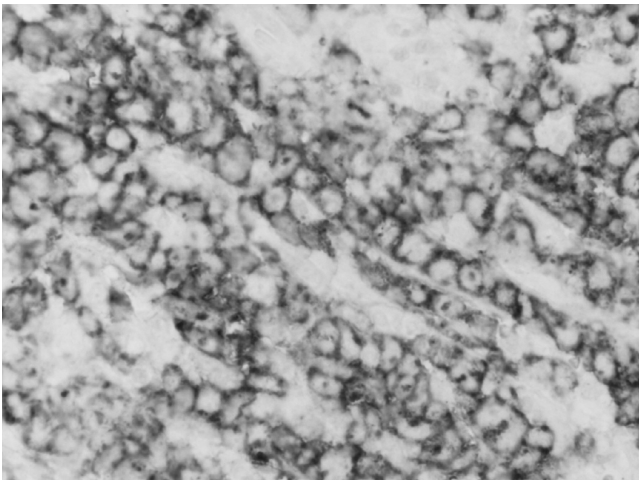


Figure-2: CD30 positive cells by IHC (x 40X).

negative for anaemia, jaundice, cyanosis, oedema or abnormal JVP. He had no cervical adenopathy. There were small 1-1.5 cms small, discrete, soft, multiple, non-tender lymph nodes in both axillae and inguinal region. The examination of respiratory, cardiovascular and nervous system was negative for any significant abnormality. Abdominal examination did not reveal any hepatosplenomegaly or abnormal mass. The scrotal examination showed both normal testes, and a small 3X2 cms ulcerative nodular lesion of right testicular skin.

His Complete Blood Count, liver function, and renal functions were within acceptable range. Urine examination confirmed haematuria, but cultures were negative for any bacterial growth. His echocardiography revealed LV dysfunction and an ejection fraction of 67%. A CT Scan was done and showed normal chest, abdomen and pelvis; except two vesical calculi measuring 3.4X2.6 cms and 3.0X3.0 cms.

An excision biopsy of scrotal ulcerative lesion was carried out. Microscopic examination showed skin with partly ulcerated epidermis, with dermis diffusely infiltrated by neoplastic lymphoid cells having nuclear pleomorphism and frequent mitoses. Some of the cells showed kidney shaped nuclei. The neoplastic cells were positive for CD3, CD43, bcl2, and CD30. They were negative for CD20, keratin, and ALK (Anaplastic lymphoma kinase). Morphologic and IHC features were those of primary cutaneous anaplastic Large cell lymphoma (ALCL, NHL T-cell type) (Figures-1 and 2). Excision was incomplete and the deep margin was positive.

A staging work up was advised including B-2-microglobulin, Lactate dehydrogenase, Uric acid, bone marrow biopsy and PET-CT. the PET-CT showed small 1.5 cms pretracheal, precarinal, and 1.8 cms right inguinal nodes which show moderate FDG uptake showing metabolically active disease. The patient was advised and has started systemic chemotherapy as per CVP-R protocol, and local radiotherapy is planned to scrotal skin due to involved margins.

A urology consultation was sought, and urologist advised treating infection at this point. They deferred any possible surgical intervention for vesical calculi till the staging work up is complete and plan of oncology management is finalized.

The patient was last seen in 3rd week of February 2011, in a good general condition. He is asymptomatic with a performance status of 0 on WHO (100 on Karnofsky) scale. He completed Local radiation therapy to the scrotum (with 6 MV photons as 3600 cGy in 16 fractions). He finished 4 doses of CVP chemotherapy protocol which he tolerated well without significant toxicity. He does not have any evidence of local or systemic disease as per clinical evaluation. His laboratory parameters (CBC, ESR, LDH, Hepatic and renal profile) are within normal range. He had a radiologic CT scan assessment (Chest, abdomen and pelvis); which showed no evidence of residual, relapse, or recurrence. A PET-CT Scan is planned which will be done shortly. He is on regular 3 monthly follow up now.

Discussion

The cutaneous T cell lymphomas (CTCL) include diverse malignancies: mycosis fungoides (MF), Sézary syndrome, lymphomatoid papulosis (LyP), anaplastic large-cell lymphoma (ALCL) and many less known varieties.¹ Clinical presentation, histology, and immunophenotype must be considered together to establish the specific subtype and ensure appropriate treatment and management.^{2,8} Diagnosis is not easy and multiple biopsies are often required.⁸ Recently recognized primary cutaneous CD30+ ALCL constitutes approximately 10 percent of all CTCL cases.² Diagnosis is

based on predominance (greater than 75%) of large clusters of CD30+ blast cells, no clinical evidence of LyP, no prior or concurrent LyP, MF, or other cutaneous lymphoma; and no extra-cutaneous lesion at presentation.^{2,6,7,9}

The primary cutaneous lymphoma (CTL) is 10% of all cutaneous lympho-proliferative disorders, with CD30+ and Negative around 5%.^{8,9} A male to female ratio in CD30+ disease is 3:2. Primary cutaneous CD30+ ALCL is a rare malignancy arising de novo in the skin and most commonly affects males in 4th-6th decade.⁹ Clinically, this condition tends to appear as a solitary nodule or tumour, often with ulceration, although 25% are multifocal at the outset.⁸ These lesions are firm, rapidly progressive, and involve trunk and extremities. Initial solitary scrotal skin lesion at presentation is not described as primary disease.² Secondary scrotal skin involvement, often high grade and after a prolonged interval, is described in literature.³

Histology is typical with clusters of infiltrating large CD30+ cells, and few peripheral inflammatory cells.^{1,4,8,9} Multinucleated cells, such as Reed-Sternberg cells, may also be seen.^{1,5} The diagnosis of primary cutaneous ALCL is based on CD30 positivity. The other tumours showing CD30+ are HL and embryonal carcinoma.⁵ It has been reported that CD30 negative LCL (having strong association with EBV) have a worse prognosis than CD30+ LCL and should be treated more aggressively. This notion has been contradicted by a European study.^{2,7}

CD30+ lesions exist as a continuum from malignant CD30+ LCL to benign LyP. The tendency of primary cutaneous CD30+ LCL to regress spontaneously in 25% cases suggests that this condition may be related to LyP.^{2,4} LyP reveals numerous inflammatory cells with few (less than 25%) CD30+ cells. This picture may be indistinguishable from some primary cutaneous CD30+ LCL, making the initial clinical presentation critical in the final diagnosis.^{3,6,8}

Primary cutaneous CD30+ LCL is histologically similar to nodal CD30+ anaplastic LCL. A diagnosis of systemic LCL is made if there is extra-cutaneous or lymph node involvement beyond regional lymph nodes.^{2,8} The subtypes of ALCL described are small cell, lymphohistiocytic, sarcomatoid, and signet ring type.¹ The differential diagnosis includes HL, metastatic Ca, B cell lymphoma, rhabdomyosarcoma, and other round blue cell tumours.¹ Systemic LCL shows a bimodal age distribution with a younger predominance associated with Epstein-Barr virus. Approximately 50 percent of cases show the t(2;5) (p23;q35) translocation (ALK - anaplastic lymphoma kinase-positive), which aids in diagnosis and to differentiate B cell lineage.^{6,7} This translocation creates NPM-ALK (Nucleophosphmin anaplastic lymphoma kinase) gene with transforming potential,⁷ while other mutations are also implicated like

defective expression of TCR, CCR8, and CCR10.¹⁰ Unlike primary cutaneous CD30+ LCL, which may remain localized for prolonged periods, this systemic counterpart with secondary cutaneous involvement is an aggressive disease with rapid spread to other organs, including the skin.^{1,8,9} It is thus imperative that metastatic systemic LCL of worse prognosis be excluded as a cause of a CD30+ cutaneous nodule, and must not be overlooked in the evaluation of CD30+ LCLs.^{1,2}

A diagnostic and staging work up should focus to determine multi focality and other systemic involvement and should include CT Scans, skin biopsy, bone marrow biopsy and RT-PCR (CD30, ALK, MUM1). Bone marrow in isolated localized skin lesions is almost always spared.¹⁰ Various therapeutic options are available for primary cutaneous CD30+ LCL depending on the extent of disease.^{1,8,9} Local radiation therapy and surgical excision are effective for limited disease, while systemic chemotherapy should be reserved for generalized disease or progression to systemic LCL.² Recently the use of IFN, thalidomide, and anti CD30 monoclonal antibody (SGN-30) is described.^{9,10} Patients with solitary localized lesions may require no treatment as spontaneous regression may occur in up to 25%.² A 5 years survival of 70-90% in ALK+ve, and 30-50% in ALK-ve cases is reported.⁴

The primary cutaneous CD30+ lymphoproliferative disorders include Anaplastic large T cell lymphoma/null-cell primary cutaneous type ALCL, lymphomatoid papulosis (LyP), and borderline cases of the EORTC classification with overlapping features of the other two conditions.^{5,10} The large atypical lymphoid cells express CD30, which is a 120 kd transmembrane cytokine receptor of the TNF receptor family being preferentially expressed by activated lymphoid cells. Originally described as strong label for Hodgkin's and Reed Sternberg cells of classical HD, CD30 is now found not specific to HD. It can also label large B cell lymphoma, other T cell lymphomas, and non-lymphoid tumours like embryonal carcinoma. ALCL is a group of large cell lymphoma of T/null cell origin strongly expressing CD30 on cell membrane and Golgi region. A definite distinction between ALCL or LyP is often difficult, and thus clinical appearance and course are used by EORTC as defining criteria.^{5,9}

Conclusion

This case is an unusual presentation of primary cutaneous CD30+ LCL as a progressive ulcero-nodular scrotal skin lesion. The scrotum, although unusual and very rare, can be a site of primary cutaneous CD30+ LCL. If a primary cutaneous CD30+ LCL is suspected, a thorough systemic evaluation is mandatory for systemic LCL and immunohistological studies for CD30- types. Ruling out these conditions will prevent unnecessarily aggressive treatment for primary cutaneous CD30+ LCL, an indolent disease with a very favourable prognosis.

Every case should be risk stratified based on prognostic factors like IPI (International prognostic index). One point is assigned for each of the risk factors: age > 60 years, stage III/IV, High Lactate dehydrogenase, ECOG performance status > 2, and more than one extra nodal sites. The cumulative points correlates with the following risk groups:

- ◆ Low risk (0-1 points) - 5-year survival of 73%
- ◆ Low-intermediate risk (2 points) - 5-year survival of 51%
- ◆ High-intermediate risk (3 points) - 5-year survival of 43%
- ◆ High risk (4-5 points) - 5-year survival of 26%

IPI is a useful clinical tool, widely used by oncologists and a mainstay of risk stratification in clinical trials for lymphoma, it should be kept in mind that it was developed prior to the use of rituximab. Rituximab has dramatically improved the outcomes of lymphoma patients, and its effect on the prognostic value of the IPI is uncertain.

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