

Case Report

CD30 expression in cutaneous B-cell and post-transplant peripheral T-cell lymphoma: report of 2 cases

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Abstract

CD30 expression is the hallmark of the cutaneous CD30+ lymphoproliferative disorders, lymphomatoid papulosis and anaplastic large cell lymphoma. We report CD30 expression in cutaneous follicle center cell lymphoma and in cutaneous post-transplant peripheral T-cell lymphoma. Histopathologists should be aware of CD30 expression in cutaneous lymphomas outside the realm of so-called CD30+ lymphoproliferative disorders to avoid diagnostic errors and improper medical treatment.

Keywords: CD30-positive T-cell lymphoma, classical Hodgkin lymphoma, CD30-positive primary cutaneous B-cell lymphoma, posttransplantation lymphoproliferative disorder of T-cell origin

Introduction

CD30, a 120 kDa glycoprotein, is a transmembrane cytokine receptor belonging to the tumor necrosis factor (TNF) receptor superfamily [1]. CD30 is normally expressed on a very small number of activated B- and T-cells, as well as some tumors such as embryonal carcinoma. Its physiological role is unclear. CD30 has been reported to be involved with negative selection of T-cells and as a co-stimulatory molecule on T-cells. In addition, CD30 may be involved in the induction of cell cycle arrest, apoptosis, and activation of the prosurvival transcription factor, NF- κ B [1]. CD30 is also highly expressed on the surface of malignant lymphocytes including those in Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL), multiple myeloma, and adult T-cell leukemia [2]. CD30 expression in cutaneous hematologic neoplasms is the hallmark of lymphomatoid papulosis and anaplastic large cell lymphoma. Separation between them requires clinical correlation and they are reported histologically under the umbrella term *CD30+ lymphoproliferative disorder*. We report two primary cutaneous lymphomas with potentially misleading CD30 expression. Neither case exhibited features of anaplastic large cell lymphoma or lymphomatoid papulosis. These cases underscore the importance of full immunophenotyping and clinical correlation for accurate diagnosis of cutaneous lymphomas. Pathologists should be aware that CD30 expression occurs in cutaneous lymphomas besides anaplastic large cell lymphoma and lymphomatoid papulosis.

Case synopsis

Case 1

A 67-year-old woman presented with several months of weakness, night sweats, 15 pound weight loss, and intractable abdominal pain. An axillary lymph node biopsy in September of 2010 demonstrated classical nodular sclerosing Hodgkin lymphoma. The patient achieved remission with ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine) by February 2011. She continued to remain in remission until May 2012 when physical examination revealed a rapidly enlarging mass in the left neck. A positron emission tomography - computed tomography (PET-CT) demonstrated abnormal activity in the neck, axilla, retroperitoneum, and inguinal area. Although a cervical lymph node biopsy performed at an outside facility was interpreted as reactive adenopathy, relapsed Hodgkin lymphoma was clinically suspected because of progressive adenopathy by imaging studies. She was treated with salvage chemotherapy with ICE (ifosfamide, carboplatin, etoposide), high-dose chemotherapy with BEAM (carmustine, etoposide, cytarabine, and melphalan) and autologous stem cell transplant. Three months post-transplant, the patient presented with multiple subcutaneous violaceous nodules across the lower abdomen, left upper thigh, and right lower leg.

Cutaneous excisional biopsy demonstrated a large dermal/hypodermal nodule comprised of small and large atypical lymphocytes (Figure 1A), some with irregular coarse nuclear membranes, vesicular nuclei, and nucleoli. There was focal tumor necrosis. The tumor was distinctly different from the patient's previous Hodgkin lymphoma. Malignant-appearing lymphocytes exhibited strongly positive CD2 and CD4 expression, moderately strongly positive CD3 and CD5 expression, and reduced CD7 expression. Large lymphocytes exhibited CD30-positive immunostaining (Figure 1B). Large lymphocytes were also granzyme B, TIA1, and Beta-F1 immunostain-positive. They were negative for CD8, CD15, CD20, CD56 and EBER, EMA, ALK1, and TCR gamma. Ki-67 antigen expression varied from 10-40% depending upon the field of examination (Figure 1). A diagnosis of peripheral T-cell lymphoma, NOS, in a post-transplant patient was rendered.

The patient was started on gemcitabine chemotherapy and demonstrated a good response with shrinking of multiple skin tumors.

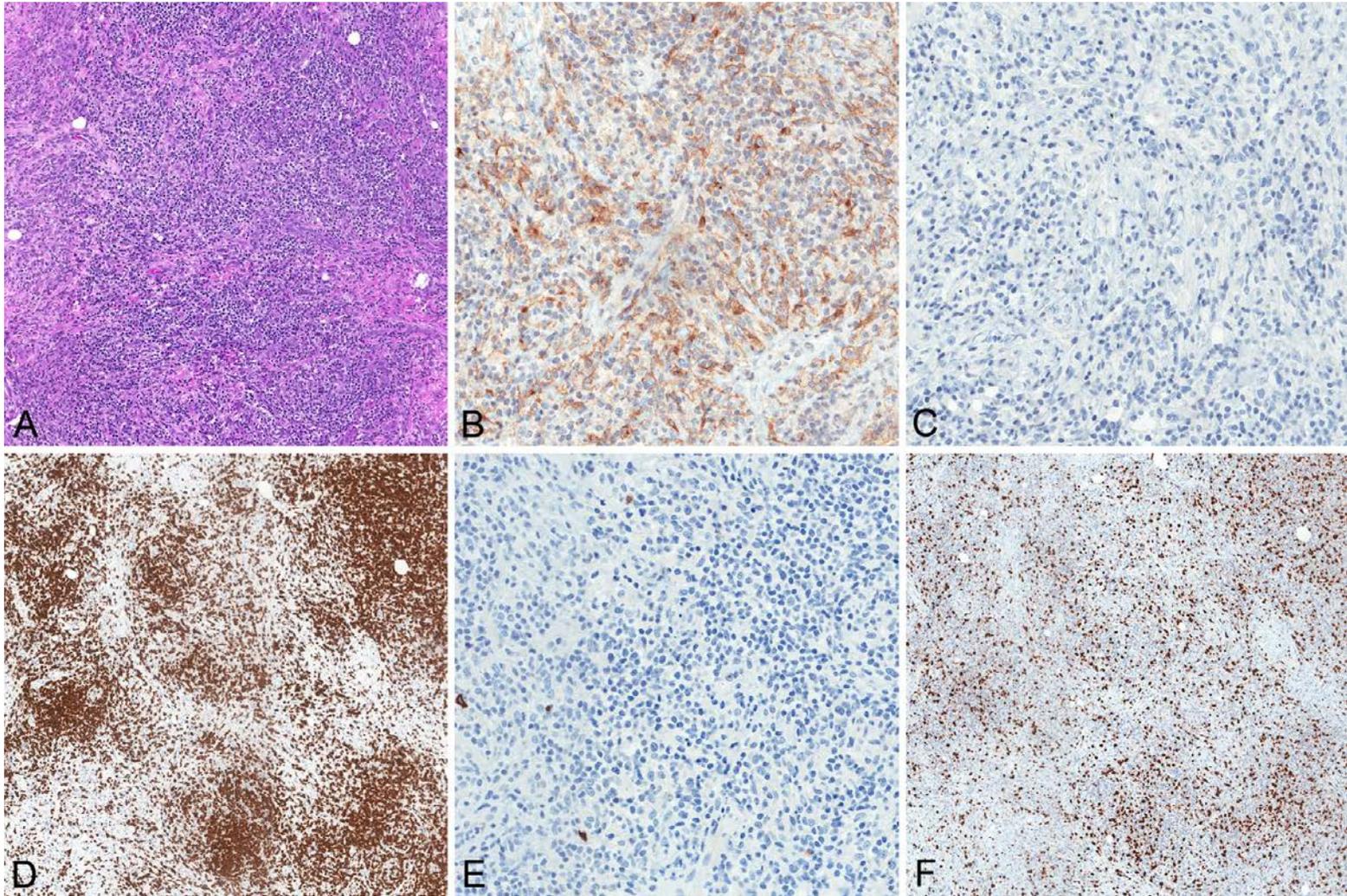


Figure 1. Peripheral T-cell lymphoma, NOS. A) Dermal/hypodermal nodule (H&E), B) showing immunoreactivity for CD30, C) negative for CD15, D) positive for CD3, E) negative for CD20, and E) Ki-67 varying from 10-40% (F).

A 64-year-old woman with a history of a subdural hematoma, reactive cervical nodal follicular hyperplasia, and 40 pound unintentional weight loss presented for evaluation of cutaneous nodules. Physical examination revealed a 5x3 cm violaceous tumor of the right external thigh. There were two smaller tumor nodules on the left thigh. Cutaneous excisional biopsy of a thigh nodule demonstrated a large dermal and partially hypodermal infiltrate comprised of large pleomorphic CD20(+) B-cells (Figure 2E) exhibiting moderately strong BCL2, BCL6, and CD30 expression, 20-25% MUM1 expression, weak CD10 expression (+/-), and absence of CD3, CD5, and IgM. Kappa and lambda *in situ* hybridization revealed sparse numbers of background polyclonal plasma cells. CD35 demonstrated meshwork of follicular dendritic cells, though discrete follicles were inconspicuous on routine hematoxylin-eosin sections (Figure 2). *In situ* hybridization for EBV (EBER) was negative. FISH for *c-myc* and t(14;18) was negative. Bone marrow biopsy was negative for lymphoma. A diagnosis of CD30-positive diffuse large B-cell lymphoma was rendered. Clinical follow-up revealed partial spontaneous regression and absence of systemic disease. The patient exhibited complete response to R-CHOP chemotherapy. We suspect this case represents a diffuse growth pattern primary cutaneous follicle center cell lymphoma with anomalous CD30 expression.

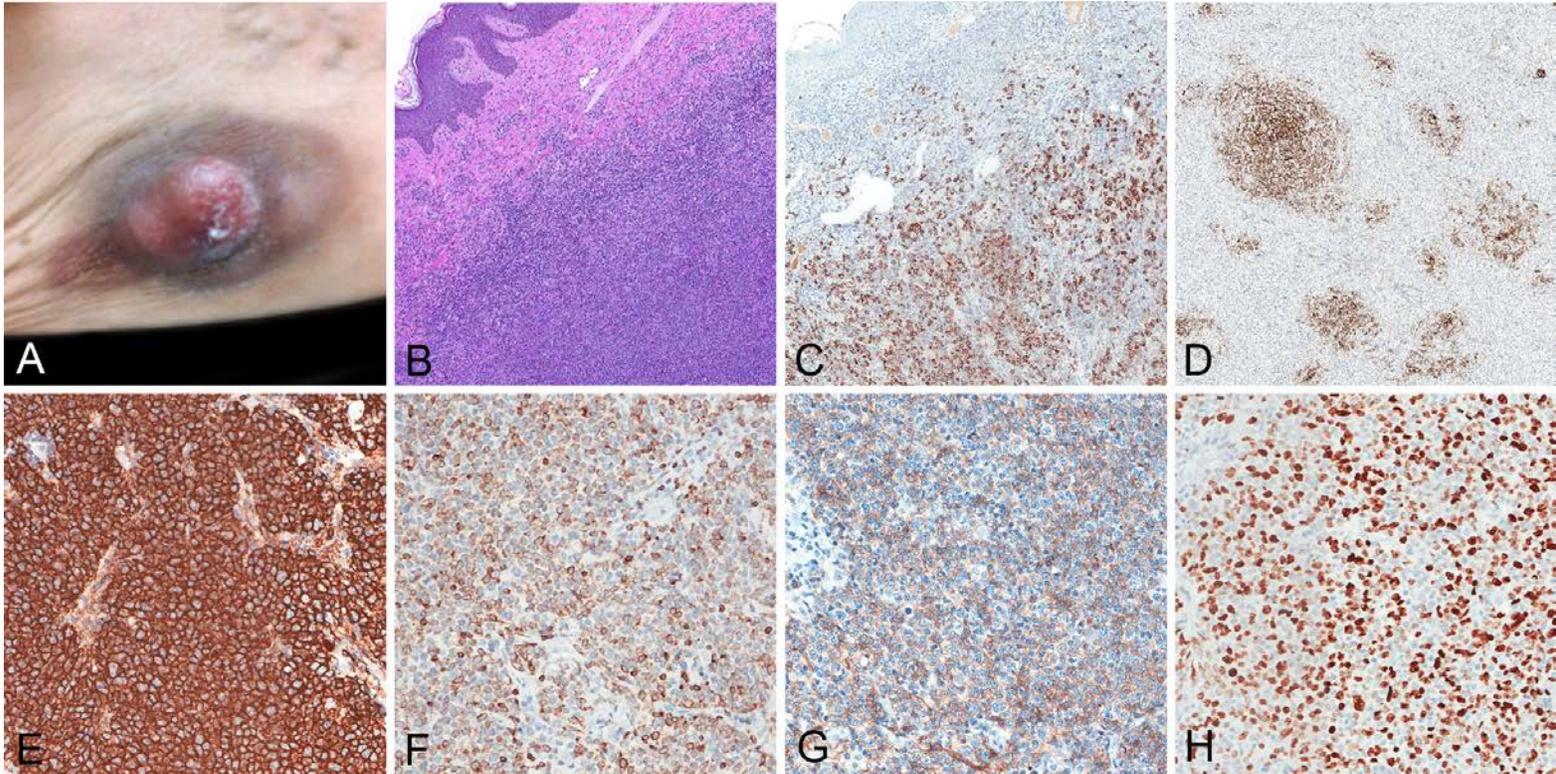


Figure 2. Primary cutaneous follicle center lymphoma. A) Thigh tumor demonstrating B) diffuse dermal infiltration (H&E), C) showing immunoreactivity for CD30, D) CD35, E) CD20, F) BCL2, G) CD10, and H) Ki-67.

Discussion

The CD30 molecule was originally identified on the surface of Reed-Sternberg cells in patients with Hodgkin lymphoma. Since then, the CD30 antigen has been identified in a variety of malignant and benign conditions. In the skin, CD30 is usually associated with lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large T-cell lymphoma (cALCL). Further, CD30 can also be positive in some cases of B cell lymphomas and mycosis fungoides [1]. CD30 is restricted to cells of the immune system including CD4+ and CD8+ T lymphocytes and is not normally expressed in resting cells of healthy individuals. CD30 regulates cell proliferation, differentiation, and apoptosis, but its exact role is not yet well understood [1,2].

Primary cutaneous CD30-positive T-cell lymphoproliferative disorders (CD30-T-LPD) are the second most common category of cutaneous T-cell lymphoma [3,8]. They include lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (c-ALCL). Some authors consider LyP and c-ALCL to be similar disorders that lie on a continuous spectrum. Separation is based upon clinical features and evolution. CD30 expression can also be encountered in large cell transformation of mycosis fungoides [8]. We describe two cases of cutaneous lymphoma in which CD30 expression might have been misconstrued as specific evidence of a CD30+ lymphoproliferative disorder. Our first case posed the differential diagnosis of a CD30+ lymphoproliferative disorder, recurrent Hodgkin lymphoma, and a de novo post-transplant T-cell lymphoproliferative disorder. The expression of T-cell-associated antigens and demonstration of a clonal T-cell gene rearrangement ruled out Hodgkin lymphoma. The absence of hallmark cells and spontaneous involution combined with the aggressive course ruled out primary cutaneous anaplastic large cell lymphoma/lymphomatoid papulosis.

Approximately 1.4% of stem cell transplant patients develop lymphoproliferative disorders [4]. Post-transplant lymphoproliferative disorders (PTLD) are divided into early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma-type PTLD [5]. Early lesions are characterized by reactive plasmacytic hyperplasia and infectious mononucleosis like lesions. Polymorphic PTLD may be either polyclonal or monoclonal and is characterized by the destruction of underlying lymphoid architecture, necrosis, and nuclear atypia. In monomorphic PTLD, the majority of cases (>80%) arise from B cells and are further subclassified as either diffuse large B-cell lymphoma or, less commonly, Burkitt/Burkitt-like lymphoma, plasma cell myeloma, or plasmacytoma-like lesions. 7% to 15% of all PTLD are of T-cell origin. See table 1 for summary of reported cases of T-cell PTLDs presenting in the skin. 91% of PTLDs involved extranodal sites, of which skin was the site in 19% of the cases [6]. 130 cases of T-cell or natural killer (NK)-cell PTLD have been reported [4,6]. Reported T-cell post-transplant lymphomas include peripheral T-cell lymphoma NOS, gamma/delta T-cell lymphoma, and T-natural killer (NK) cell varieties [5,6]. T/NK-cell PTLDs occur at a median of 66 months following transplantation [6]; 91% manifest at extranodal sites, particularly the skin (91%). Approximately one third are Epstein-Barr virus (EBV) positive with a significantly longer survival of 18 months vs 6 month survival in EBV negative cases [6]. Treatment varies, but usually consists of chemotherapy with decreased immunosuppression, sometimes combined with irradiation [6].

Table 1. Reported cases of T-cell PTLDs presenting in the skin

Case	Site	Diagnosis	Transplant	EBV	Age, sex
Yurtsever et al 2003 ¹⁴	Lower leg and draining lymph nodes	T-anaplastic large cell lymphoma	Renal	-	59, male
Coyne et al 2004 ¹⁵	Abdomen, chest, back, arms, and thigh	T-anaplastic large cell lymphoma	Renal	+	33, female
Coyne et al 2004 ¹⁵	Medial malleolus and lower leg	T-anaplastic large cell lymphoma	Renal	-	56, male
Coyne et al 2004 ¹⁵	Upper posterior chest wall	T-anaplastic large cell lymphoma	Renal	+	52, male
Salama 2006 ¹⁶	Leg	T-anaplastic large cell lymphoma	Renal	-	59, male
Mills et al 2012 ¹⁷	Skin and lung	Monomorphic T-cell PTLD and mycosis fungoides	Renal	-	17, male

Our second case demonstrates CD30 expression in a cutaneous B-cell neoplasm. Primary cutaneous B-cell neoplasms with CD30 expression are rare in the literature [7]. We suspect the lack of reports in the literature may reflect low usage of CD30 immunostaining in B-cell neoplasms rather than intrinsic absence of the antigen in this subset of lymphomas. The differential diagnosis of diffuse large B cell lymphoma of the skin includes primary cutaneous diffuse large B-cell lymphoma (PCDLBCL), leg type, PCDLBCL, other, and cutaneous follicle center lymphoma (PCFCL) with diffuse growth pattern [9]. PCFCL is the most common primary cutaneous B-cell lymphoma. It afflicts older adults (median age in the 6th decade), with a male predilection (male to female ratio of 1-2:1) [10]. Most patients present with lesions on the scalp/forehead or trunk, but other cutaneous sites can be involved, including the leg [11]. PCFCL has a 5-year survival >95% and is not affected by the number of tumors, recurrences, or the histological growth pattern. Location on the legs is associated with a poorer prognosis in PCFCL [9,12]. PCDLBCL, leg type is an aggressive lymphoma of activated B-cell post-germinal center origin, with 5-year survival of 50% [9]. It afflicts older adults (mean age 78 years), with a female predominance. PCDLBCL, leg type manifests with rapidly growing nodular tumors, which can ulcerate, can appear on one or both legs, and rarely present above the lower extremities [9].

Separation of these lymphomas is difficult and requires supplementary immunohistochemical and molecular studies. B-cells of germinal center origin are CD20(+), CD79a(+), bcl-6(+) and bcl-2(-), whereas activated postgerminal B cells are bcl-2(+), MUM-1(+), FOXP1(+), and bcl-6(±) [9]. PCFCL is diagnosed when there is a predominance of large cleaved cells, sometimes admixed with small and medium sized centrocytes, and expression of germinal center cell markers such as bcl-6 and less frequently CD10 [9]. PCDLBCL, leg type is diagnosed when there is a preponderance of large, round cells expressing IgM/BCL2/IRF4/MUM-1 [9]. We classified our case as PCFCL because of the presence of large pleomorphic CD20(+) B-cells exhibiting moderately strong BCL2 and BCL6, with weak staining for MUM1 and CD10, and absence of staining for CD3, CD5, and IgM. Systemic chemotherapy was utilized because of the known aggressive behavior in PCFCL when located on the leg.

CD30-positive cells can also be found in a variety of nonneoplastic skin disorders. Large atypical CD30-positive lymphocytes are described in cutaneous viral infections such as orf, herpes simplex and varicella zoster dermatitis, HIV, and molluscum contagiosum. CD30 positive lymphocytes have also been reported in nodular scabies, leishmaniasis, and syphilis [13]. Many infectious agents are able to induce the presence of CD30-positive lymphocytes in the skin; clinicopathologic correlation is mandatory to avoid misdiagnosis.

In summary, we describe two cutaneous lymphomas with CD30 expression outside the realm of so-called CD30+ lymphoproliferative disorder. Histopathologists should be aware that CD30 expression in cutaneous lymphomas is not unique to either lymphomatoid papulosis or anaplastic large cell lymphoma.

References

1. Schlaf G, Altermann WW, Rothhoff A, Seliger B. Soluble CD30 serum level--an adequate marker for allograft rejection of solid organs? *Histol Histopathol.* Nov 2007; 22(11):1269-79. [PMID:17647199]
2. Wright CW, Rumble JM, Duckett CS. CD30 activates both the canonical and alternative NF-kappaB pathways in anaplastic large cell lymphoma cells. *J Biol Chem.* Apr 2007;282(14): 10252-62. [PMID:17261581]
3. Eberle FC, Song JY, Xi L, Raffeld M, Harris NL, Wilson WH, Pittaluga S, Jaffe ES. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. *Am J Surg Pathol.* May 2012;36(5):716-25. [PMID:22367293]
4. Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robinson LL. New malignancies after blood or marrow stem cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol.* 2003;21:1352-1358. [PMID:12663726]
5. LaCasce AS. Post-transplant lymphoproliferative disorders. *Oncologist* 2006;11:674-680. [PMID:16794246]
6. Swerdlow SH. T-cell and NK-cell posttransplantation lymphoproliferative disorders. *Am J Clin Pathol.* 2007 Jun;127(6):887-95. [PMID:17509986]
7. Herrera E, Gallardo M, Bosch R, Cabra B, Aleri V, Sánchez P. Primary cutaneous CD30 (Ki-1)-positive non-anaplastic B-cell lymphoma. *J Cutan Pathol.* Mar 2002;29(3):181-4. [PMID:11972717]
8. Kadin ME, Drews R, Samel A, Gilchrist A, Kocher O. Hodgkin's lymphoma of T-cell type: clonal association with a CD30+ cutaneous lymphoma. *Hum Pathol.* 2001;32:1269-1272. [PMID:11727269]
9. Demirkesen C, Tuzuner N, Esen T, Lebe B, Ozkal S. The expression of IgM is helpful in the differentiation of primary cutaneous diffuse large B cell lymphoma and follicle center lymphoma. *Leukemia Research.* Jun 2011;35(9):1269-1272. [PMID:21700336]
10. Fernandez-Flores A, Smucler-Simonovich A, Escalante F, Manjon JA. The differential diagnosis between primary cutaneous large B-cell lymphoma and cutaneous follicular lymphoma: prognostic and therapeutic implications. *Am J Dermatopathol.* Dec 2011;33(8):819-26. [PMID:22042259]
11. Hristov AC. Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type: Diagnostic Considerations. *Arch Pathol Lab Med.* Aug 2012; 136(8):876-881. [PMID:22849734]
12. Kempf W, Denisjuk N, Kerl K, Cozzio A, Sander C. Primary cutaneous B-cell lymphomas. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft.* Jan 2012;10(1):12-23. [PMID:22212142]
13. Werner B, Massone C, Kerl H, Cerroni L. Large CD30-positive cells in benign, atypical lymphoid infiltrates of the skin. *J Cutan Pathol.* 2008;35:1100-7. [PMID:18616762]
14. Yurtsever H, Kempf W, Laeng RH. Posttransplant CD30+ anaplastic large cell lymphoma with skin and lymph node involvement. *Dermatology.* 2003;207(1):107-10. [PMID:12835569]
15. Coyne JD, Banerjee SS, Bromley M, Mills S, Diss TC, Harris M. Post-transplant T-cell lymphoproliferative disorder/T-cell lymphoma: a report of three cases of T-anaplastic large-cell lymphoma with cutaneous presentation and a review of the literature. *Histopathology.* Apr 2004;44(4):387-93. [PMID:15049906]
16. Salama S. Primary "cutaneous" T-cell anaplastic large cell lymphoma, CD30+, neutrophil-rich variant with subcutaneous panniculitic lesions, in a post-renal transplant patient: report of unusual case and literature review. *Am J Dermatopathol.* Jun 2005;27(3):217-23. [PMID:15900125]
17. Mills KC, Sangüeza OP, Beaty MW, Raffeld M, Pang CS. Composite B-cell and T-cell lineage post-transplant lymphoproliferative disorder of the lung with unusual cutaneous manifestations of mycosis fungoides. *Am J Dermatopathol.* Apr 2012;34(2):220-5. [PMID:22214855]