

Common Imitators of Subcutaneous Panniculitis-like T-Cell Lymphoma

Tatsiana Pukhalskaya^{*}, Hatice B. Zengin and Bruce R. Smoller

Department of Pathology and Laboratory Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

Abstract

The differential diagnosis of a lobular panniculitis without vasculitis can be extensive. This review article is based on a case we recently described and is aimed to address the most common variants of lobular panniculitis that could be mistaken for Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL). The neoplastic lymphocytes express CD8+ with rearranged an α/β subunit of the T-cell receptor. Cytotoxic markers are always expressed (TIA1, perforin, and granzyme B), but CD56 and CD30 are consistently negative

Keywords: Cutaneous • Panniculitis • Lupus Erythematosus Panniculitis (LEP) • Factitial panniculitis

Introduction

Firstly, we would like to discuss the most serious and life-threatening of all non-infectious Subcutaneous Panniculitides-Subcutaneous Panniculitis-like T-Cell Lymphoma (SPTCL) [1]. It is a cutaneous lymphoma originating from cytotoxic CD8+ α/β T-lymphocytes and presenting as a form of panniculitis [2]. It is thought that the unique pathophysiology is due to the CCR5 receptor on the neoplastic T cells that facilitates their migration to the targeted adipocytes [3]. This disease affects young adults who commonly present with a long history of "benign panniculitis" [4].

Clinically SPTCL presents as single or multiple cutaneous nodules and plaques and rarely as alopecia [5]. In a minority of cases it might be accompanied by systemic symptoms i.e. fever, malaise, fatigue and weight loss or hemophagocytic syndrome [6]. The lesions are mainly located on the extremities, especially the lower ones. Other sites of the body, including the head, may be affected [4]. The lesions are painless and usually do not ulcerate. In its early phase, the nodules may spontaneously resolve without treatment and new nodules may develop on the same or different skin locations [7-9]. Usually there is a slow progression of the disease with an 80% 5-year survival rate [10,11].

Literature Review

Classically SPTCL is characterized by lobular panniculitis with a sparing of interlobular septa, the epidermis, and dermis [12] (Figure 1). However, interface dermatitis, peri-adnexal inflammation and dermal mucin deposition can be identified, creating a marked similarity to Lupus Erythematosus Panniculitis or Lupus Profundus (LEP) [13]. The hallmark of the atypical process is a dense, nodular or diffuse lobular infiltrate of small, medium or large pleomorphic cells [14]. The neoplastic T-lymphocytes have irregular hyperchromatic nuclei and are arranged in small clusters or solitary units around the single adipocyte i.e. "rimming of the adipocytes" [14]. It has been demonstrated that this finding of "rimming" is not specific and is also seen in cases of lupus panniculitis. It should be noted that in the beginning of the disease, the lymphocytic infiltrate may be less atypical [4]. Occasionally large phagocytic histiocytes containing cell debris or red blood cells are seen. Karyorrhexis, mitoses, and fat necrosis are commonly seen [2]. Reactive small lymphocytes might also be present in the neoplastic infiltrate, but plasma cells and eosinophils are rare [14].

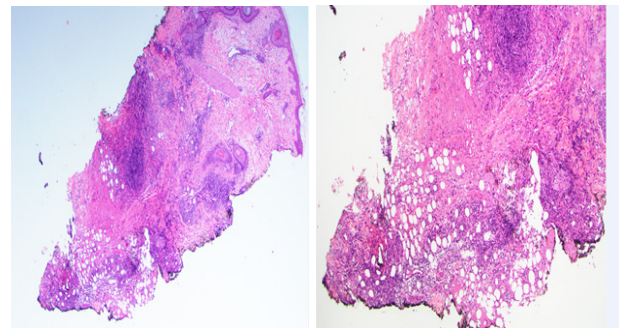


Figure 1. H and E x 20 - SPTCL. This figure demonstrates lobular infiltrate of atypical lymphocytes.

The neoplastic lymphocytes express CD8+ with rearranged an α/β subunit of the T-cell receptor. Cytotoxic markers are always expressed (TIA1, perforin, and granzyme B), but CD56 and CD30 are consistently negative [13]. EBV is mostly negative but has been found in some cases of SPTCL, where it is possibly associated with hemophagocytic syndrome [15,16]. The genomic studies have also shown this disease to be associated with gains of 5q and 13q chromosome [17].

The first and most crucial differential diagnosis that comes into play with SPTCL is lupus erythematosus panniculitis. The challenge of the differential diagnosis between LEP and SPTCL lies in clinical and histological similarities between the two conditions. Antinuclear antibodies and other criteria for the diagnosis of systemic lupus erythematosus may be absent in some cases, adding extra difficulty in the diagnostic dilemma.

Lupus Erythematosus Panniculitis (LEP) is considered a unique entity within the lupus spectrum. In contrast to other variants of the disease, LEP is characterized by prominent involvement of the subcutaneous tissue [14]. It may occur as a separate condition or in association with Discoid Lupus Erythematosus (DLE) or Systemic Lupus Erythematosus (SLE) [18]. In the majority of cases, it tends to have a mild chronic course marked by recurrent nodules or plaques. LEP usually affects a middle-aged population (40-50 years) with a female preponderance [18]. A slightly younger age group (20-40 years) is affected in the Asia and Africa [19-21].

Clinically it is characterized by subcutaneous plaques and indurations,

***Corresponding Author:** Tatsiana Pukhalskaya, Department of Pathology and Laboratory Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA, E-mail: tatsiana_pukhalskaya@urmc.rochester.edu

Copyright: © 2021 Pukhalskaya T, et al. This is an open-access article distributed under the terms of the creative commons attribution license which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Received: February 16, 2020; **Accepted:** March 03, 2021; **Published:** March 10, 2021

mostly located on the trunk, lower back and proximal extremities [22]. Similar to SPTCL, lesions on the scalp have been reported [23]. Large, painful, indolent ulcers may also develop [24].

There has been a controversy regarding the specificity of histopathologic findings in LEP [25]. Nevertheless, it usually shows a predominantly lobular panniculitis (Figure 2). In half of the cases there are epidermal and dermal changes of lupus erythematosus with basal vacuolar change and a superficial and deep perivascular lymphocytic infiltrate with perifollicular involvement [13]. Mucin deposition may also be found. Lymphocytic nuclear dust within a patchy lymphoplasmacytic infiltrate in the fat lobules and hyaline fat necrosis are commonly observed [26] (Figure 3). Other clues for the histopathologic diagnosis of LEP include the presence of lymphoid follicles in the subcutaneous tissue adjacent to fibrous septa as well as plasma cells, eosinophils and lipophages within the inflammatory infiltrate [26,27]. Although the later are not pathognomonic of LEP, these findings are not observed in SPTCL [28]. A relatively useful feature for the histological differentiation between LEP and SPTCL is the presence of "rimming" of fat cells by pleomorphic atypical T-lymphocytes, although "rimming" phenomena has been described in several cases of LEP [14, 28]. Interestingly, CD123 positive plasmacytoid dendritic cells were found to be a characteristic feature of LEP and not SPTCL [29]. In addition, different patterns of fat necrosis may be observed in these entities (hyaline and lipomembranous in lupus panniculitis and fibrinoid/coagulative in SPTCL) [29]. Unfortunately, monoclonal T-cell receptor rearrangement has been also found in cases of LEP [28]. This emphasizes the extreme difficulties in attempting to distinguish these two entities in some cases.

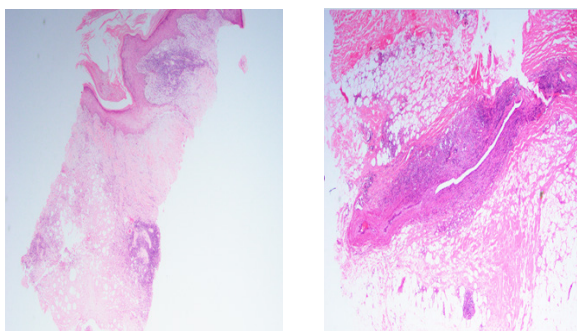


Figure 2. H and E x 20-This figure demonstrates lobular infiltrate of lupus panniculitis.

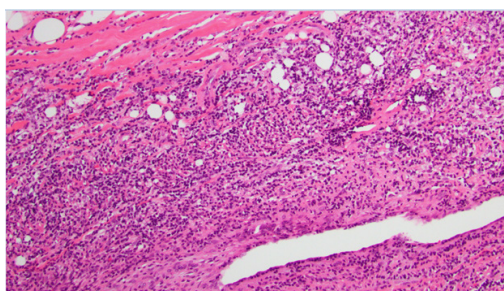


Figure 3. H and E x 100-This figure demonstrates mixed lobular infiltrate of lupus panniculitis.

Traumatic Panniculitis (TP) might be clinically and histologically mistaken for SPTCL or LEP. It refers to changes in the subcutaneous fat related to various types of trauma [30] the causes are both physical and chemical. There is a single reported case of panniculitis induced by cupping therapy [31]. It is assumed that most cases of this are not biopsies as the etiology of the clinical changes can be ascertained. When a cause is not identified it might be referred to cryptogenic panniculitis [1]. In addition, many cases of traumatic fat necrosis have a factitial origin and overlap with factitial panniculitis [32].

This condition can occur at any age and is usually self-limiting. It is not specific in its clinical presentation but in various circumstances might mimic SPTCL and LEP [30]. Cutaneous lesions are commonly tender and

represent indurated and warm subcutaneous plaques or nodules.

Discussion

In general, it is believed that the extent of the severity of the adipose tissue response to trauma is not related to the intensity of the injury [33]. Nevertheless, it results in dermal and hypodermal changes in the form of predominantly lobular panniculitis [34]. The histologic findings include fat microcysts surrounded by histiocytes, collections of foam cells, and mixed types of inflammatory cells. Later lesions may develop fibrosis, lipomembranous (membranocystic) changes, dystrophic calcium deposits or ectopic calcification [30]. Although the histology of TP might mimic more serious conditions, the clinical picture as well as the mixed population of the inflammatory cells in the infiltrate and lack of monoclonality helps to elucidate the correct diagnosis.

Factitial Panniculitis (FP) is a form of traumatic panniculitis that follows injection of foreign material into the subcutaneous fat [13]. This type of panniculitis is associated with a factitious disorder and is seen more frequently in females [35]. It may be induced by a broad variety of injected substances milk, urine, feces, oils, drugs, etc. Sclerosing lipogranuloma (paraffinoma) is a particular form of factitial panniculitis that develops after the injection of lipid (often paraffin) into the subcutaneous tissue for a presumed cosmetic purposes [36].

FP is characterized by bizarre patterns of cutaneous changes that might be clinically misleading [35]. The lesions commonly arise on areas easily accessible to the patient and present as painful rubbery indurations of the affected area or hard nodules and plaques. Symmetrical distribution is not frequent [37]. Some cases may show abscess formation, lymphangitic spread, skin sloughing, contractures, and deformities [37]. Fistulas and ulcerations are common due to focal liquefaction of the fat and its further discharge through a surface wound [38]. Small tissue spaces may develop after transdermal fat elimination [13]. Local lymph nodes might be enlarged [37].

The diagnosis of factitial lesions is made largely by exclusion of other potential entities since patients often deny the action of self-harm [37]. Skin biopsies frequently reveal all skin layers to be involved by the process [35]. The histopathological features of factitious panniculitis often include a pattern of lobular inflammation with a predominantly neutrophilic infiltrate in early lesions and a more granulomatous infiltrate at a later stage [39]. There might be tissue "holes" from the foreign material deposition that was eliminated during the processing. Other patterns such as suppurative septal panniculitis can occur [35]. Foreign body giant cells containing foreign material may be present [13]. In paraffinomas and oleomas there is a characteristic Swiss-cheese appearance with disruption of fat cells and their replacement by cystic spaces of variable size with predominantly septal distribution of lymphocytes and lipid-containing macrophages and foreign body giant cells (sclerosing lipogranuloma) [40].

Finally, in rare cases, a chronic subtype of alpha-1 antitrypsin deficiency might come into the differential diagnosis and mimic a more serious process. Alpha-1 Antitrypsin Deficiency Panniculitis (A1AT). It is a well-established entity that is characterized by low serum levels of alpha-1 antitrypsin and autosomal recessive inheritance [13]. The tissue absence of A1AT results in uncontrolled activation of lymphocytes and macrophages, lack of restraint for complement and the accumulation of neutrophils [41] this leads to uncontrolled secondary tissue damage. Susceptibility of the subcutis to A1AT deficiency is based on the high density of fatty acids that make elastin more susceptible to degradation [42]. Other systemic manifestations of the deficiency include emphysema, neonatal hepatitis, cirrhosis, pancreatitis and membranoproliferative glomerulonephritis [41].

Most cases present during the third and fourth decades of life [43]. The prevalence of this condition is equal in both sexes, and no racial predominance had been described. Interestingly, panniculitis may be an

early sign of this disorder [13]. It begins with tender, erythematous and indurated subcutaneous nodules on the trunk and extremities and might occasionally mimic cellulitis [42, 44]. The new lesions are commonly triggered by trauma or childbirth [45,46]. The nodules tend to ulcerate spontaneously and to heal with atrophic scars [13,41].

In the beginning of the process neutrophils extend into the reticular dermis resulting in an infiltrate between the collagen bundles [41]. That is followed by dissolution of dermal collagen with transepidermal elimination of the liquefied material [47]. Later, an acute panniculitis, predominantly lobular, is observed with an abundance of neutrophils and some necrosis of fat cells [48]. There also may be collagenolysis of the fibrous septa with further formation of isolated adipocyte lobules [44]. Skip-areas of normal fat adjacent to foci of severe necrotizing panniculitis are characteristic [48]. Vasculitis is sometimes present in the subcutis (different than aforementioned entities). Later lesions might show collections of histiocytes and lipophages as well as variable fibrosis and rarely dystrophic calcifications [49].

Conclusion

Overall, we believe that correct diagnosis of a lobular panniculitis can be quite challenging. The diagnostic approach to this destructive cutaneous inflammatory process should be based on the integration of all available information concerning the clinical presentation, histopathology, immunohistochemistry, and molecular studies (when available).

References

- Pukhalskaya, Tatsiana, Brown J Ahmad, Sills Adam A and Smoller Bruce R. "A Longstanding, Persistent and Recurrent Case of Cryptogenic Panniculitis." *Case Rep Dermatol* 12(2020):199-208.
- Parveen, Zahida and Thompson Karen. "Subcutaneous Panniculitis-like T-cell Lymphoma: Redefinition of Diagnostic Criteria in the Recent World Health Organization-European Organization for Research and Treatment of Cancer Classification for Cutaneous Lymphomas." *Arch Pathol Lab Med* 133(2009):303-308.
- Fujii Kazuyasu. "New Therapies and Immunological Findings in Cutaneous T-Cell Lymphoma." *Front Oncol* 8(2018):198.
- Hoque SR, Child FJ, Whittaker SJ and Ferreira S. "Subcutaneous Panniculitis-like T-cell Lymphoma: A Clinicopathological, Immunophenotypic and Molecular Analysis of Six Patients." *Br J Dermatol* 148(2003):516-525.
- Torok L, Gurbity TP, Kirschner A and Krenacs L. "Panniculitis-like T-cell Lymphoma Clinically Manifested as Alopecia." *Br J Dermatol* 147(2002):785-788.
- Heyman, Benjamin and Beaven Anne. "Mycophenolate Mofetil for the Treatment of Subcutaneous Panniculitis-Like T-Cell Lymphoma: Case Report and Review of the Literature." *Clin Lymphoma Myeloma Leuk* 18(2018):e437-e440.
- Sugeeth MT, Narayanan G, Jayasudha AV and Nair RA. "Subcutaneous Panniculitis-like T-cell Lymphoma." *Proc (Bayl Univ Med Cent)* 30(2017):76-77.
- Santucci, Marco, Pimpinelli Nicola, Massi Daniela and Kadin Marshall E, et al. "Cytotoxic/natural Killer Cell Cutaneous Lymphomas: Report of EORTC Cutaneous Lymphoma Task Force Workshop." *Cancer* 97(2003):610-627.
- Perniciaro C, Zalla MJ, Jr White JW and Menke DM. "Subcutaneous T-cell Lymphoma. Report of two Additional Cases and Further Observations." *Arch Dermatol* 129(1993):1171-1176.
- Massone, Cesare, Lozzi Gian Piero, Egberts Friederike and Fink-Puches Regina. "The Protean Spectrum of Non-Hodgkin Lymphomas with Prominent Involvement of Subcutaneous Fat." *J Cutan Pathol* 33(2006):418-425.
- Marzano, Angelo V, Berti Emilio and Paulli Marco. "Cytophagic Histiocytic Panniculitis and Subcutaneous Panniculitis-like T-cell Lymphoma: Report of 7 Cases." *Arch Dermatol* 136(2000):889-896.
- Musick, Sierra R and Lynch David T. "Subcutaneous Panniculitis Like T-cell Lymphoma." *StatPearls. Treasure Island (FL)* (2020).
- Patterson James. "Weedon's Skin Pathology." Elsevier (2020).
- Cerroni, Lorenzo, Gatter Kevin BM, Kerl Helmut and DPhil. "An Illustrated Guide to Skin Lymphoma." Blackwell Publishing (2004).
- Wang L, Yang Y, Liu W and Li G, et al. "Subcutaneous Panniculitis-like T-cell Lymphoma: Expression of Cytotoxic-granule-associated Protein TIA-1 and its Relation with Epstein-Barr Virus Infection." *Zhonghua Bing Li Xue Za Zhi* 29(2000):103-106.
- Iwatsuki K, Harada H, Ohtsuka M and Han G, et al. "Latent Epstein-Barr Virus Infection is Frequently Detected in Subcutaneous Lymphoma Associated with Hemophagocytosis but not in Nonfatal Cytophagic Histiocytic Panniculitis." *Arch Dermatol* 133(1997):787-788.
- Hahtola, Sonja, Burghart Elke, Jeskanen Leila and Karenko Leena, et al. "Clinicopathological Characterization and Genomic Aberrations in Subcutaneous Panniculitis-like T-cell Lymphoma." *J Invest Dermatol* 128(2008):2304-2309.
- Tuffanelli, Denny L. "Lupus Erythematosus Panniculitis (Profundus)." *Arch Dermatol* 103(1971):231-242.
- Watanabe T and Tsuchida T. "Lupus Erythematosus Profundus: A Cutaneous Marker for a Distinct Clinical Subset?" *Br J Dermatol* 134(1996):123-125.
- Winkelmann RK. "Panniculitis in Connective Tissue Disease." *Arch Dermatol* 119(1983):336-344.
- Ng, Patricia Pei-Lin, Tan Suat Hoon and Tan Tulip. "Lupus Erythematosus Panniculitis: A Clinicopathologic Study." *Int J Dermatol* 41(2002):488-490.
- Peters MS and Su WP. "Lupus Erythematosus Panniculitis." *Med Clin North Am* 73(1989):1113-1126.
- Kossard, Steven. "Lupus Panniculitis Clinically Simulating Alopecia Areata." *Australas J Dermatol* 43(2002):221-223.
- Tamada Y, Arisawa S, Ikeya T and Yokoi T, et al. "Linear Lupus Erythematosus Profundus in a Young Man." *Br J Dermatol* 140(1999):177-178.
- Fountain RB. "Lupus Erythematosus Profundus." *Br J Dermatol* 80(1968):571-579.
- Massone, Cesare, Kodama Kazuo, Salmhofer Wolfgang and Abe Riichiro, et al. "Lupus Erythematosus Panniculitis (Lupus Profundus): Clinical, Histopathological, and Molecular Analysis of Nine Cases." *J Cutan Pathol* 32(2005):396-404.
- Peters MS and Su WP. "Eosinophils in Lupus Panniculitis and Morphea Profunda." *J Cutan Pathol* 18(1991):189-192.
- Magro CM, Crowson AN, Kovatich AJ and Burns F. "Lupus Profundus, Indeterminate Lymphocytic Lobular Panniculitis and Subcutaneous T-cell Lymphoma: A Spectrum of Subcuticular T-cell Lymphoid Dyscrasia." *J Cutan Pathol* 28(2001):235-247.
- Liau, Jau-Yu, Chuang Shih-Sung, Chu Chia-Yu and Ku Wen-Hui, et al. "The Presence of Clusters of Plasmacytoid Dendritic Cells is a Helpful Feature for Differentiating Lupus Panniculitis from Subcutaneous Panniculitis-like T-cell Lymphoma." *Histopathology* 62(2013):1057-1066.
- Moreno, Abelardo, Marcoval Joaquim and Peyri Jordi. "Traumatic Panniculitis." *Dermatol Clin* 26(2008):481-483.
- Moon, Suk-Ho, Han Hyun-Ho and Rhie Jong-Won. "Factitious Panniculitis Induced by Cupping Therapy." *J Craniofac Surg* 22(2011):2412-2414.
- Winkelmann RK and Barker SM. "Factitious Traumatic Panniculitis." *J Am Acad Dermatol* 13(1985):988-994.
- Shellagi, Nikhil and Rodrigues Gabriel. "Traumatic Panniculitis of the Right Thigh: A Case Report." *Oman Med J* 26(2011):436-437.
- Requena, Luis. "Normal Subcutaneous Fat, Necrosis of Adipocytes and Classification of the Panniculitides." *Semin Cutan Med Surg* 26(2007):66-70.
- Oh CC, McKenna DB, McLaren KM and Tidman MJ. "Factitious Panniculitis Masquerading as Pyoderma Gangrenosum." *Clin Exp Dermatol* 30(2005):253-255.

36. Oertel YC and Johnson FB. "Sclerosing Lipogranuloma of Male Genitalia. Review of 23 Cases." *Arch Pathol Lab Med* 101(1977):321-326.
37. Sarica, Ozgur, Kayhan Arda, Demirkürek Hüseyin Cengiz and Igdem Ayşenur Akyıldız. "Subcutaneous Oleomas Following Sunflower Oil Injection: A Novel Case and Review of Literature." *J Breast Health* 12(2016):141-144.
38. Pehlivano G, Kavaklieva S, Kazandjieva J and Kapnilov D, et al. "Foreign-Body Granuloma of the Penis in Sexually Active Individuals (Penile Paraffinoma)." *J Eur Acad Dermatol Venereol* 22(2008):845-851.
39. Requena, Luis and Yus E Sanchez. "Panniculitis. Part II. Mostly Lobular Panniculitis." *J Am Acad Dermatol* 45(2001):325-361.
40. Claudy A, Garcier F and Schmitt D. "Sclerosing Lipogranuloma of the Male Genitalia: Ultrastructural Study." *Br J Dermatol* 105(1981):451-456.
41. Valverde, Ricardo, Rosales Belén, Frutos Francisco Javier Ortiz-de and Rodríguez-Peralto José Luis, et al. "Alpha-1-Antitrypsin Deficiency Panniculitis." *Dermatol Clin* 26(2008):447-451.
42. Smith KC, Pittelkow MR and Su WP. "Panniculitis Associated with Severe Alpha 1-Antitrypsin Deficiency. Treatment and Review of the Literature." *Arch Dermatol* 123(1987):1655-1661.
43. Edmonds BK, Hodge JA and Rietschel RL. "Alpha 1-Antitrypsin Deficiency-Associated Panniculitis: Case Report and Review of the Literature." *Pediatr Dermatol* 8(1991):296-299.
44. Hendrick SJ, Silverman AK, Solomon AR and Headington JT. "Alpha 1-Antitrypsin Deficiency Associated with Panniculitis." *J Am Acad Dermatol* 18(1988):684-692.
45. Yesudian PD, Dobson CM and Wilson NJ. "Alpha1-Antitrypsin Deficiency Panniculitis (Phenotype PiZZ) Precipitated Postpartum and Successfully Treated with Dapsone." *Br J Dermatol* 150(2004):1222-1223.
46. Linares, Barrios M, Conejo-Mir IS, Igarza J L Artola and Navarrete M. "Panniculitis due to Alpha 1-Antitrypsin Deficiency Induced by Cryosurgery." *Br J Dermatol* 138(1998):552-553.
47. Pittelkow MR, Smith KC and Su WP. "Alpha-1-Antitrypsin Deficiency and Panniculitis. Perspectives on Disease Relationship and Replacement Therapy." *Am J Med* 84(1988):80-86.
48. Su WP, Smith KC, Pittelkow MR and Winkelmann RK. "Alpha 1-Antitrypsin Deficiency Panniculitis: a Histopathologic and Immunopathologic Study of Four Cases." *Am J Dermatopathol* 9(1987):483-490.
49. Gaillard MC, Bothwell J and Dreyer L. "A Case of Systemic Nodular Panniculitis Associated with M1 (Val213) Z Phenotype of Alpha 1-Protease Inhibitor." *Int J Dermatol* 36(1997):278-280.

How to cite this article: Pukhalskaya, Tatsiana, Hatice B. Zengin and Bruce R. Smoller. "Common Imitators of Subcutaneous Panniculitis-like T-Cell Lymphoma." *J Cosmo Trichol* 7(2021) :149.