

Review

Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) in Elderly, the Importance of a Sport Activity Training

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Short title: pcALCL in elderly and sport activity

Abstract : PcALCL mainly concerns elderly patients. It is a large CD30+ T-cell neoplasm composed of large cells with anaplastic, pleomorphic or immunoblastic morphology, with exclusively cutaneous onset and localization. The clinical course of pcALCL is predominantly indolent. Most elderly patients with lymphoma tend to have a sedentary lifestyle, which has a negative effect on their quality of life (QoL) and on their survival. Several studies indicate that exercise has a positive impact on QoL because it reduces peak oxygen consumption, improves physical capacity, increases self-esteem, reduces accumulated stress and promotes relaxation. Therefore, particularly in indolent lymphomas, it is necessary to indicate a program of physical activity to be practiced systematically. The complete surgical excision and local radiotherapy are the first line gold standard in pcALCL with solitary lesion.

Keywords: cutaneous lymphoma in elderly; skin tumors; T-cell lymphomas; sport activity training

1. Introduction

PcALCL is a large CD30+ T-cell neoplasm composed of large cells with anaplastic, pleomorphic or immunoblastic morphology, with an exclusive cutaneous localization [1]. The clinical course of pcALCL is predominantly indolent, completely, different from that of the systemic forms of ALCL [2]. Anaplastic large cell lymphomas (ALCL) are a group of T-cell lymphoproliferative diseases characterized by the presence of anaplastic cells with CD30 positivity and by a variable expression of T cell markers [3]. Neoplastic cells defined as "hallmark cells" are morphologically distinguishable as large pleomorphic cells with abundant cytoplasm and eccentric kidney-shaped nuclei. These are common aspects of all kinds of ALCL, but each type differs from the others for clinical presentation, prognosis, and molecular features. According to the last revision of WHO (2016) [4], ALCL are classified as ALK positive large cell anaplastic lymphoma (ALK+ ALCL), ALK negative ALCL (ALK- ALCL), Breast Implant-Associated ALCL (BI- ALCL) and pcALCL. The first two forms have a systemic clinical presentation and development with lymphadenomegaly, splenomegaly, hepatomegaly, secondary extranodal infiltration mainly involving the skin, bones, soft tissues, and lungs, associated with systemic symptoms like fever, weight loss, and night sweats. Central nervous system involvement is rare. At the onset, of illness it is common to find an already widespread disease in stage III-IV according to Ann Arbor, with systemic symptoms (B). ALK + ALCL is more common in adolescents and children. ALK- ALCL has a higher incidence in adults over 60 years. Both forms have an unfavorable prognosis, the ALK+ being worse under 40 years. ALK- DUSP22 + subtype appears to have a better prognosis.

BI-ALCL is a form localized in areas adjacent to the breast implant. It generally has an indolent course, a good prognosis. Morphologically comparable to the other forms, it is ALK- with an excellent response to surgical therapy. However, systemic development of this type is also known, characterized by an unfavorable prognosis like the above described systemic forms.

Patients with pcALCL are diagnosed at an older age, but it may involve also children. Males are more often affected than females (ratio 3:1). About 25% of patients have the DUSP22-IR4 locus at onset, while TP63 rearrangements are rare. Unlike systemic forms, both chromosomal aberrations do not appear to be related to a worse prognosis [5].

Support in patients with lymphoma is essential to avoid depression, reduction of self-esteem, and the onset of unreal emphasis of symptoms like fatigue and pain [6-7]. It is striking how most cancer patients have a sedentary lifestyle, which can have a negative effect on their quality of life (QoL) [8-9]. In addition, several studies indicate that physical activity has a positive impact on QoL in cancer survivors [10-11], because it reduces peak oxygen consumption, improves physical capacity, increases self-esteem, reduces accumulated stress and promotes relaxation [12]. Physical activity also plays a favorable effect on metabolism, inflammation and the immune system [13]. In particular, it regulates macrophages and natural killer lymphocytes widely involved in interactions with cancer cells [14-15]. In addition, randomized studies have highlighted how physical activity in cancer patients may improve the QoL [16-18]. In our department we encourage patients a progressively increase and a program of physical activity, depending on their physical abilities and attitudes. Such physical activity includes sports activities, planned exercise, domestic activities, professional activities and walks. The main objective of this review will be to describe all new diagnostic and therapeutic features of primary cutaneous ALCL with regard to the elderly patient and to evaluate the importance of physical activity.

2. Etiology and Pathogenesis

It has been hypothesized that cutaneous pcALCL is the result of chronic T-cell activation by Langerhans cell-mediated antigen presentation, like in eczema and dermatopathic lymphadenopathy. Pc-ALCL is associated with 2;5 chromosomal traslocation, the 3' half of ALK, derived from chromosome 2 and coding for the catalytic domain, is fused to the 5' portion of NPM from chromosome 5. The product of the NPM-ALK fusion gene is oncogenetic. Antigens associated with insect bites can attract T-lymphocytes on the skin, some of which carry the ALK t (2;5) translocation. The subsequent release of several cytokines at the puncture site could act as a

determinant and activate T cells, which can express the NPM-ALK oncogenic protein and initiate deregulated growth. It is noted that the loss of transforming growth factor-beta (TGF- β) induced lymphocyte growth inhibition and dysregulation of TGF- β /SMAD signaling may be brought in transformation from lymphomatoid papulosis (LyP) to pcALCL [19]. There are a lot of studies about the role in the pathogenesis of CD30+lymphoproliferative disorders (EBV, HHV8, *Clamydophila pneumoniae*, *Borrelia burdoferi*, HTLV 1) but anything specific for pc-ALCL was found. Carbamazepine-associated PC-ALCL had also been documented [20].

3. Clinical Presentation

For most patients the disease begins with a single skin nodular lesion (Figure 1), often ulcerated, with a diameter of more than 2 cm, while, for 20% of patients the onset multiple localizations on different skin areas (Figure 2). The clinical features of skin lesions are nodules, papules, plaques, cellulitis-like ulcerations, their color ranges from red to violaceous, may rapidly grow and have predilection for head, neck and extremities. Generally, the disease is asymptomatic and fevers, night sweats or weight loss are usually lacking. Spontaneous regressions have been reported for 10–42% of lesions. PcALCL may be the result of mycosis fungoides (MF) progression [21]. Therefore, in patients with pcALCL, a current or previous diagnosis of MF should be excluded. The differential diagnosis between pcALCL and CD30 + MF transformed can be even more difficult when there is a clinical presentation with a previous or simultaneous patch-plaque MF stage. The presence of multiple lesions in 20% of the cases can make difficult the differential diagnosis with the type C LyP, which presents borderline lesions [21,22]. The onset with multiple sites and major extension appears to have worse prognosis due to a higher incidence of cases with evolution to secondary cutaneous ALCL (scALCL). The international Society of the Cutaneous Lymphomas European Organization for Research and Treatment of Cancer proposed on the tumor, node, metastases (TNM) classification of cutaneous lymphoma other than mycosis fungoides and Sezary syndrome (Table 1) [21]. This classification is based on the size of the lesions, on the skin areas involved, on the lymph node stations involved, on the extranodal and visceral localizations. It is clearly usable for staging of both pcALCL and scALCL. Staging is essential to distinguish the pcALCL from scALCL (Table 1). All patients at diagnosis should perform a complete metabolic panel, LDH, Tc-PET, since these exams allow to exclude a systemic infiltration from ALCL.



Figure 1. Histological features of Pc-ALCL. A) This skin punch biopsy is characterized by a dense lymphoid population filled the dermis, without significant epidermotropism. The epidermis shows secondary changes including hyperkeratosis and papillomatosis (H&E, 2.4x). Inset: the neoplastic population is composed by large-sized cells with abundant slightly eosinophilic cytoplasm and roundish, atypical nuclei. Two mitotic figures are evident in the center of the field. Some neutrophils and eosinophils are scattered in the context of the neoplastic population (H&E, 20x). The large cells are positive for CD3 (B), CD4 (C) and CD30 (D) immunohistochemical staining.



Figure 2. Clinical presentation of ALK- pcALCL with extensive ulcerated plaques located on the trunk and upper arms (a). Resolution of skin lesions, with central scarring and depigmentation after treatment. (b).

Table 1. ISCL/EORTC TNM classification of cutaneous lymphomas other than MF/SS.

Skin (T)	T1	Solitary skin involvement
	T1a	Solitary lesion <5 cm diameter
	T1b	Solitary lesion ≥ 5 cm diameter
T2	Regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions	
	T2a	All disease encompassing a <15 cm diameter circular area
	T2b	All disease encompassing a 15 to ≤ 30 cm diameter circular area
	T2c	All disease encompassing a ≥ 30 cm diameter circular area
T3		Generalized skin involvement
	T3a	Multiple lesions involving 2 noncontiguous body regions
	T3b	Multiple lesions involving ≥ 3 body regions
Lymph nodes (N)	N0	No clinical or pathologic lymph node involvement
	N1	Involvement of one peripheral or central lymph node region that drains an area of current or prior skin involvement
	N2	Involvement of ≥ 2 peripheral or central lymph node regions or involvement of any lymph node region that does not drain in an area of current or prior skin involvement
	N3	Involvement of central lymph nodes
Viscera (M)	M0	No evidence of extracutaneous non-lymph node disease
	M1	Extracutaneous non-lymph node disease present

Adapted from Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a proposal of the

International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007;110(2):480. [22].

3.1. Histological and Molecular Features

The classical form of pcALCL is characterized by a nodular infiltrate of large lymphoid cells, mostly confined to the dermis, usually without epidermotropism (Figure 3). However, several histological variants have been described like that rich in neutrophils and eosinophils (which are scattered in the classical form), more common in immunosuppressed patients. The angiocentric form, the angiolytic form, the subcutaneous and keratoacanthoma-like form, the sarcomatoid variants with prevalent spindle-cell morphology, the small cells and intravascular ALCL form. The cell phenotype is usually characterized by a positivity for CD30 (75% in tumor cells), CD3, CD4, CD45RO, and no expression for CD5 and CD2. In about 50% of cases, it has been described a positivity for CD71, HLA-DR and CD25 (IL-2R), TIA1, perforin and granzyme B, for cutaneous lymphocyte antigen (CLA, HECA-452). Positive EMA is only focal, unlike the systemic ALK- ALCL strongly expresses this marker. KIR3DL2 (CD158k) from neoplastic cells is expressed, as in Sézary syndrome. Another important feature that very useful for diagnostics is the alteration of the receptor complex of T/CD3 cells, the transcription factors associated with T receptors and signal transduction molecules, a frequent finding in CD30+, systemic and cutaneous lymphoproliferative diseases. The monoclonal rearrangement of the TCR gene is present in 65-90% of cases. The majority of pcALCLs are ALK-, DUSP22-, TP63-. However, other mutations may also occur, particularly considering the frequency order: DUSP22 rearrangement, ALK translocations, TP63 rearrangements and NPM1-TYK2 gene fusion [24]. The DUSP22 rearrangements are related to a particular histological pattern characterized by the simultaneous presence of two different clones: one large CD30+ cells infiltrating the dermis, and another characterized by small CD30+ lymphoid cells with a pattern of pagetoid reticulosis. It has been shown that the expression of the chemokine receptor gene CCR8 is associated with DUSP22 rearrangements in ALCL. It is possible that the higher expression level of this receptor will explain the lower tendency of pcALCL to disseminate in extracutaneous sites, contained by the limiting action of the immune system. The presence or not of the DUSP22 rearrangement does not change the prognosis. In contrast to sALCL, the cases of ALK+ pcALCL seem to have a favorable outcome, comparable to that of patients with ALK- pcALCL. The TP63 rearrangement has long been studied because previously associated with very aggressive cases of the disease. Subsequent studies do not seem to have confirmed the specificity of this rearrangement in the rapidly evolving forms. Other mutations seem to have a relationship with the evolution of the disease, including those on the path JAK1 / STAT3. These mutations were found only in 5% of pcALCL. It is well known that deregulation of Notch signaling in hematopoietic cells is linked to the development of various hematological malignancies, including chronic B-cell lymphocytic leukemia, acute T-cell lymphoblastic leukemia, acute myeloid leukemia, multiple myeloma, sALCL and Hodgkin's lymphoma. Also, the pcALCL neoplastic cells have an increased expression of the intracellular domains of Notch1, Notch2, Notch3 and Notch4 receptors, as well as of the HES1 product and the Delta ligand. The inhibition of gamma-secretase with specific inhibitors has been shown to induce apoptosis and decrease cell viability in the pcALCL cell lines, inhibiting the Notch pathway. Therefore, this is to be considered as a potential target to be considered in the near future for the therapies of these diseases.

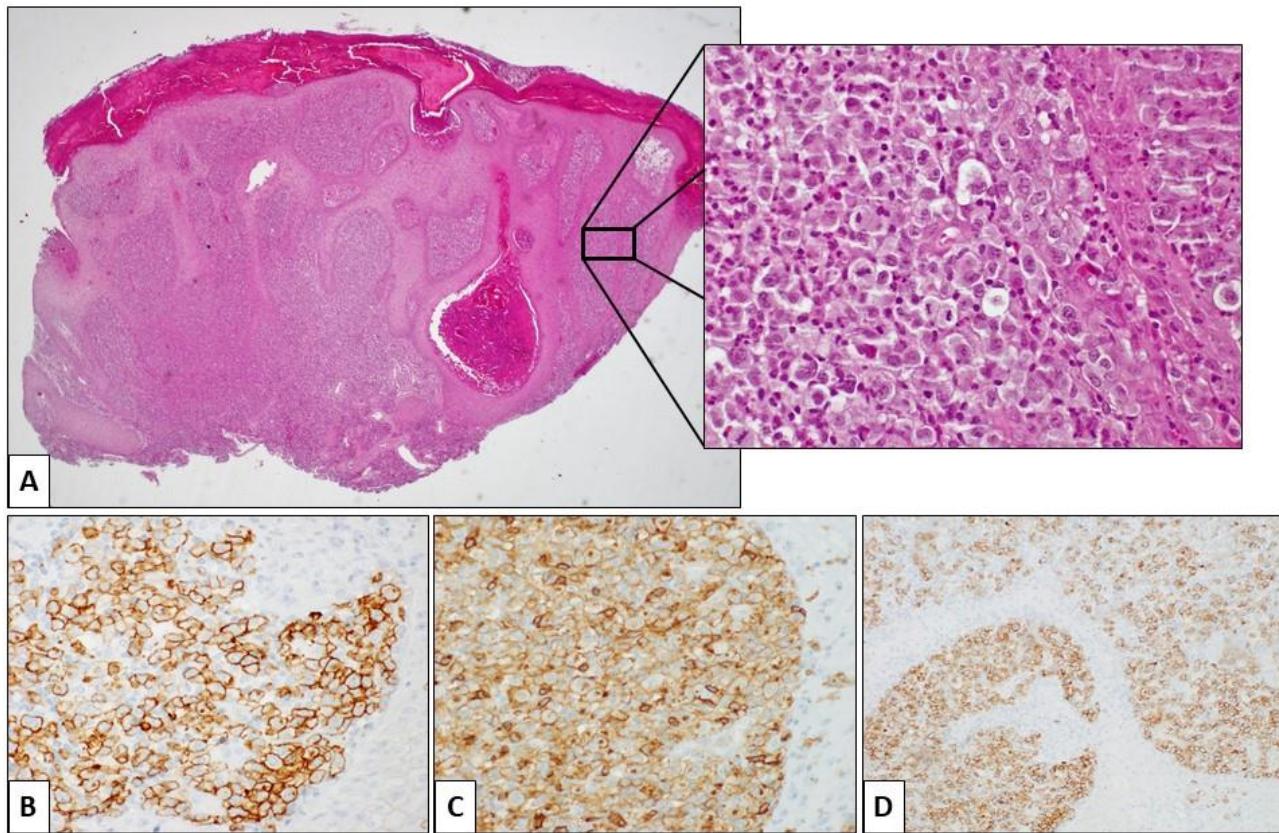


Figure 3. ALK- pcALCL single localization on a leg.

3.3. Cytogenetic Alterations.

The following chromosomal alterations are characteristic and recurrent in this type of lymphoma: the gains of 7q31 and losses in the 6q16-6q21, 6q27 and 13q34 regions.

4. Differential Diagnosis

The most important differential diagnosis for a pcALCL is definitely with the sALCL. The systemic form occurs with an isolated involvement of cutaneous lymphatics, or the cutaneous form may be the most evident clinical manifestation of a systemic (scALCL). For this reason, the first step for definitive diagnosis of pcALCL requires the exclusion of the first. The morphology and immunophenotypic characteristics of LyP (in particular type C) and pcALCL overlap significantly and no biomarker has so far been able to reliably distinguish these two entities, so it is essential to correlate the pathological results with the history clinic that represent the only distinctive elements. In fact, it is the clinical behavior of LyP, characterized by recurrent episodes and by the onset of papules and nodules sometimes at spontaneous resolution, which helps in the distinction between the two pathologies. Another very similar pathology is MF with large cell transformation (MF-LCT), among other things also CD30+. Patients with MF-LCT typically have classical, long-lasting lesions of MF, with the development of tumor nodules, while patients with pcALCL tend to be younger with less disease-related skin spread and more rare truncal involvement. The prognosis of MF-LCT is much more severe, with a 20-year overall survival of 20%. From a histopathological point of view, MF-LCT is characterized by epidermotropic or dermal aggregates of CD30+ tumor cells that occur less frequently in pcALCL. The expression of GATA3+ is more frequent in MF-LCT, while the perforin is more expressed in pcALCL. Adult T-cell lymphoma (ATCL) may show diffuse CD30 expression and nuclear pleomorphism similar to pcALCL, but the presence of HTLV-1 in the former is pathognomonic. Other entities that enter the differential diagnosis of pcALCL include B-cell lymphoma and cutaneous leukemia. Some cases of diffuse large cell B-lymphoma CD30+, anaplastic variant, may represent a diagnostic challenge, especially if CD20 and CD79a are

negative. Classical syncytial nodular sclerosis Hodgkin's lymphoma (NSCHL) is another disease to consider, although pcALCL can rarely express CD30 and CD15 simultaneously, and CD45 is positive in most pcALCL and negative in NSCHL. Leukemia cutis may also show pcALCL-like histology but usually expresses TdT, CD34 and / or CD117 and myeloid lineage markers such as myeloperoxidase.

5. Therapies

The complete surgical excision and local radiotherapy are the first line gold standard therapy of pcALCL with solitary or grouped localized lesions (up to T2N0M0) [25]. In the more advanced stage of the illness with cutaneous dissemination and in the relapsing/refractory disease, the administration of brentuximab vedotin (BV), an anti-CD30 antibody-conjugate, has shown low toxicity and a high percentage of remissions and has been recommendable in the elderly patient [26-27]. Methotrexate and bexarotene are further indicated therapeutic options [28-30]. Appropriate screening for HCV and HBV infection should be performed to prevent any flare-ups of viral hepatopathies [31-35]. The γ -secretase inhibitors (inhibition of the Notch pathway) and the JAK1/2/3 inhibitors that are effective in vitro to control the cell growth of the pcALCL has been also suggest for the more advanced stages of the illness [36]. Other proposed are the anti-ALK molecules such as crizotinib, alectinib and ceritinib, which in pcALCL patients with ALK rearrangements could downregulate the STAT3 pathway, inducing apoptosis. The IPH4102, a humanized monoclonal antibody directed against the KIR3DL2 cell receptor (CD158K) has been also proposed. Finally, histone deacetylase (HDAC) inhibitors (romidepsin and vorinostat) and demethylating agents have demonstrated efficacy in inducing cell cycle arrest, differentiation and / or apoptosis of tumor cells [37-41].

6. Discussion and Conclusion

PcALCL is a lymphoma with a good prognosis and low mortality, which mainly concerns the elderly. Unfortunately, several patients have had multiple relapses throughout their clinical history, particularly in forms with diffuse skin localization in multiple body districts [42]. The history of these patients is therefore characterized by many therapeutic lines. The chemotherapy protocols used for this subset of patients are variable. Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) is one of the most widely used protocols and has an overall response rate (ORR) of 85%. Other regimens well tolerated by the elderly with comorbidities are: cyclophosphamide, vincristine and prednisone (CVP); oral etoposide, gemcitabine and methotrexate at low doses or in monotherapy [43-45]. All these regimens are valid therapeutic options in this subset of patients, although they have shown a high frequency of relapses. The efficacy of BV that has a 75% ORR seems different, with fast response and good tolerability even in older patients. The most common adverse event described is peripheral sensory neuropathy. The diagnosis of pcALCLs is particularly difficult because its clinical presentation is variable. In addition, its histological and molecular characteristics also show numerous affinities with similar lymphoproliferative pathologies with the prognosis and therapy are completely different. For this reason, it is so important to study the patient from an anamnestic and clinical point of view to arrive at a correct diagnosis assisted by all the available molecular, genetic and histological investigations. The therapy should also consider eventual comorbidities of patients who in most cases are elderly, and consider a physical activity program. The physical activity programme to be recommended to elderly patients aims to generate positive feelings and optimism and consider the disease as a moment of transition to face and overcome. It is not easy for those patients who already suffer from comorbidities [46-47], but helps to keep the musculoskeletal and circulatory system in good functional condition, to eliminate excess body fat and to stimulate the regulatory function of the immune system on macrophages, NK cells, cytokine production and other factors involved in cancer prevention. In addition, movement improves energy and hormone metabolism, reduces inflammation, and, finally, it helps to stay in good shape with an improved self-esteem [48].

Funding: This research received no external funding.

Conflicts of Interest: All the authors of the manuscript declare they have no conflict of interest in connection with this paper.

Competing Interests: The authors have declared that no competing interests exist.

References

1. Nikolaenko, L.; Zain, J.; Rosen, S.T.; Querfeld, C. CD30-Positive Lymphoproliferative Disorders. *Cancer Treat Res.* **2019**;176:249–268.
2. Melchers, R.C.; Willemze, R.; Bekkenk, M.W.; de Haas, E.R.M.; Horvath, B.; van Rossum, M.M.; Sanders, C.J.G.; Veraart, J.C.J.M.; Vermeer, M.H.; Quint, K.D. In a multifunctional primary cutaneous anaplastic large cell lymphoma: report of the Dutch Cutaneous Lymphoma Group. *Br J Dermatol.* **2018**; 179 (3): 724–731.
3. Kaseb, H.; Rajasurya, V. Cancer, Anaplastic Large Cell Lymphoma (ALCL Ki 1+). SourceStatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; **2018-2019** Jan.
4. Lynch, R.C.; Gratzinger, D.; Advani, R.H. Clinical Impact of the 2016 Update to the WHO Lymphoma Classification. *Curr Treat Options Oncol.* **2017**;18(7):45. doi: 10.1007/s11864-017-0483-z. Review. Erratum in: *Curr Treat Options Oncol.* **2017**;18(10):60.
5. Willemze, R.; Cerroni, L.; Kempf, W.; Berti, E.; Facchetti, F.; Swerdlow, SH.; Jaffe, ES. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood.* **2019**. pii: blood-2018-11-881268.
6. Melton, L.; Brewer, B.; Kolva, E.; Joshi, T.; Bunch, M. Increasing access to care for young adults with cancer: results of a quality-improvement project using a novel telemedicine approach to supportive group psychotherapy. *Palliat Support Care.* **2017**; 15: 176–180.
7. Fischetti, F.; Greco, G.; Cataldi, S.; Minoia, C.; Loseto, G.; Guarini, A. Effects of Physical Exercise Intervention on Psychological and Physical Fitness in Lymphoma Patients. *Medicina (Kaunas).* **2019**;55(7). pii: E379. DOI: 10.3390/medicina55070379.
8. Courneya, K.S.; Sellar, C.M.; Stevenson, C.; McNeely, M.L.; Peddle, C.J.; Friedenreich, C.M.; Tankel, K.; Basi, S.; Chua, N.; Mazurek, A.; et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *J. Clin. Oncol.* **2009**;27:4605–4612. DOI: 10.1200/JCO.2008.20.0634.
9. Lucía, A.; Earnest, C.; Pérez, M. Cancer-related fatigue: Can exercise physiology assist oncologists? *Lancet Oncol.* **2003**;4:616–625. DOI: 10.1016/S1470-2045(03)01221-X.
10. Dimeo, F.C. Effects of exercise on cancer-related fatigue. *Cancer.* **2001**;92:1689–1693.
11. Oldervoll, L.M.; Kaasa, S.; Knobel, H.; Loge, J.H. Exercise reduces fatigue in chronic fatigued Hodgkin's disease survivors—Results from a pilot study. *Eur. J. Cancer.* **2003**;39:57–63. DOI: 10.1016/S0959-8049(02)00483-5.
12. Cramp, F.A.; Byron-Daniel, J.Z. Exercise for the management of cancer related fatigue in adults. *Cochrane Database Syst. Rev.* **2012**;11. DOI: 10.1002/14651858.CD006145.pub3.
13. Knols, R.; Aaronson, N.K.; Uebelhart, D.; Fransen, J.; Aufdemkampe G. Physical exercise in cancer patients during and after medical treatment: A systematic review of randomized and controlled clinical trials. *J. Clin. Oncol.* **2005**;23:3830–3842. DOI: 10.1200/JCO.2005.02.148.
14. Blair, C.K.; Morey, M.C.; Desmond, R.A.; Cohen, H.J.; Sloane, R.; Snyder, D.C.; Demark-Wahnefried, W. Light-intensity activity attenuates functional decline in older cancer survivors. *Med. Sci. Sports Exerc.* **2014**;46:1375. DOI: 10.1249/MSS.0000000000000241.
15. Craig, CL.; Marshall, AL.; Sjostrom, M.; et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* **2003**; 35:1381e95.
16. Minoia, C.; Ciavarella, S.; Lerario, G.; Daniele, A.; De Summa, S.; Napolitano, M.; Guarini, A. Improvable Lifestyle Factors in Lymphoma Survivors. *Acta Haematol.* **2018**;139(4):235–237. DOI: 10.1159/000489252.
17. Global Recommendations on Physical Activity for Health. WHO Library Cataloguing-in-Publication Data 2010; © World Health Organization. ISBN 978 92 4 159 997 9.
18. Sica A, Casale B, Di Dato MT, Calogero A, Spada A, Sagnelli C et al. Cancer and not cancer related chronic pain: from the physiopathological bases to the management. *Open Med (Wars).* **2019**;14:761-766. doi: 10.1515/med-2019-0088.

19. Sica, A.; Vitiello, P.; Sorriento, A.; Ronchi, A.; Calogero, A.; Sagnelli, C.; Troiani, T.; Fasano, M.; Dodaro C.A.; Franco, R.; Casale, B.; Santangelo, M.; Ciccozzi, M.; Ciardiello, F.; Argenziano, G.; Moscarella, E. Lymphomatoid papulosis. *Minerva Medica* in press
20. Di Lernia, V.; Viglio, A.; Cattania, M.; Paulli, M. Carbamazepine-induced, CD30+, primary, cutaneous, anaplastic large-cell lymphoma. *Arch Dermatol.* **2001**;137(5):675-676.
21. Kim Y.H, Willemze R, Pimpinelli N, Whittaker S, Olsen E.A, Ranki A, Dummer R, Hoppe R.T.; ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood.* **2007**;110(2):479-84.
22. Gerami, P.; Wickless, S.C.; Rosen, S.; Kuzel, T.M.; Ciurea, A.; Havey, J.; Guitart, J. Applying the new TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome in primary cutaneous marginal zone lymphoma. *J Am Acad Dermatol.* **2008**;59(2):245-54. DOI: 10.1016/j.jaad.2008.04.012.
23. Caccavale, S.; Vitiello, P.; Franco, R.; Panarese, I.; Ronchi, A.; Sica, A.; Jurakic, T.R.; Alfano, R.; Argenziano, G. Dermoscopic characterization of folliculotropic mycosis fungoides selectively localized on trunk and limbs. *Int J Dermatol.* **2019**;58(10):e187-e189. DOI: 10.1111/ijd.14490.
24. Prieto-Torres, L.; Rodriguez-Pinilla, S.M.; Onaindia, A.; Ara, M.; Requena, L.; Piris, M.Á. CD30-positive primary cutaneous lymphoproliferative disorders: molecular alterations and targeted therapies. *Haematologica.* **2019**; 104 (2): 226-235.
25. Reginelli, A.; Belfiore M.P.; Russo, A.; Turriziani, F. ; Moscarella, E. ; Troiani, T. ; Brancaccio G., Ronchi, A., Giunta, E., Sica A., Iovino, F., Ciardiello, F., Franco, R., Argenziano, G., Grassi R., Cappabianca, S. A preliminary study for quantitative assessment with HFUS (High Frequency ultrasound) of nodular skin melanoma Breslow thickness in adults before surgery: Interdisciplinary team experience. *Curr Radiopharm.* **2019**. DOI: 10.2174/1874471012666191007121626.
26. Duvic, M.; Tetzlaff, MT.; Gangar, P.; Clos, AL.; Sui, D.; Talpur, R. Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis. *J Clin Oncol.* **2015**;33(32):3759-3765.
27. Prince, H.M.; Kim, Y.H.; Horwitz, S.M.; et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet.* **2017**;390(10094):555-566. 69.
28. Shinohara, M.M.; Shustov, A. How I treat primary cutaneous CD30+ lymphoproliferative disorders. *Blood.* **2019**. pii: blood.2019000785. DOI: 10.1182/blood.2019000785.
29. Kempf, W.; Pfaltz, K.; Vermeer, M.H.; 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.
30. Bekkenk, M.W.; Geelen, F.A.; van Voorst Vader, P.C.; 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.
31. Pisaturo M.; Guastafierro S.; Filippini P.; Tonziello G.; Sica A.; Di Martino F.; Sagnelli C.; Ferrara M.G.; Martini S.; Cozzolino D.; Sagnelli E.; Coppola N. Absence of occult HCV infection in patients experiencing an immunodepression condition. *Infez Med.* **2013**;21(4):296-301.
32. Tonziello, G.; Pisaturo, M.; Sica, A.; Ferrara, MG.; Sagnelli, C.; Pasquale, G.; et al. Transient reactivation of occult hepatitis B virus infection despite lamivudine prophylaxis in a patient treated for non-Hodgkin lymphoma. *Infection.* **2013**;41(1):225-9. DOI: 10.1007/s15010-012-0305-y.
1. Coppola, N.; Pisaturo, M.; Guastafierro, S.; Tonziello, G.; Sica, A.; Iodice, V.; et al. Increased hepatitis C viral load and reactivation of liver disease in HCV RNA-positive patients with onco-haematological disease undergoing chemotherapy. *Dig Liver Dis.* **2012**;44(1):49-54. DOI: 10.1016/j.dld.2011.07.016.
2. Coppola, N.; Pisaturo, M.; Guastafierro, S.; Tonziello, G.; Sica, A.; Sagnelli, C.; et al. Absence of occult hepatitis C virus infection in patients under immunosuppressive therapy for oncohematological diseases. *Hepatology.* **2011**;54(4):1487-9. DOI: 10.1002/hep.24436.
33. Merli, M.; Frigeni, M.; Alric, L.; Visco, C.; Besson, C.; Mannelli, L.; Di Rocco, A.; Ferrari, A.; Farina, L.; Pirisi, M.; Piazza, F.; Loustaud-Ratti, V.; Arcari, A.; Marino, D.; Sica, A.; Goldaniga, M.; Rusconi, C.; Gentile, M.; Cencini, E.; Benanti, F.; Rumi, M.G.; Ferretti, V.V.; Grossi, P.; Gotti, M.; Sciarra, R.; Tisi, M.C.;

Cano I.; Zuccaro V.; Passamonti, F.; Arcaini, L.; Direct-Acting Antivirals in Hepatitis C Virus-Associated Diffuse Large B-cell Lymphomas. *Oncologist*. 2018; pii: theoncologist.2018-0331. DOI: 10.1634/theoncologist.2018-0331.

34. Matutes, E. The 2017 WHO update on mature T- and natural killer (NK) cell neoplasms. *Int J Lab Hematol*. 2018;40 Suppl 1:97-103. DOI: 10.1111/ijlh.12817.

35. Woo, D.K.; Jones, C.R.; Vanoli-Storz, M.N.; et al. Prognostic factors in primary cutaneous anaplastic large cell lymphoma: characterization of clinical subset with worse outcome. *Arch Dermatol*. 2009;145(6):667-674.

36. Bekkenk, M.W.; Geelen, F.A.; van Voorst Vader, P.C.; et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up of 219 patients and guidelines for diagnosis and treatment. *Blood*. 2000;95(12):3653-3661.

37. Woo, D.K.; Jones, C.R.; Vanoli-Storz, M.N.; et al. Prognostic factors in primary cutaneous anaplastic large cell lymphoma: characterization of clinical subset with worse outcome. *Arch Dermatol*. 2009;145(6):667-674.

38. Welborn, M.; Duvic, M. Antibody-Based Therapies for Cutaneous T-Cell Lymphoma. *Am J Clin Dermatol*. 2019;20(1):115-122.

3. Sica, A.; Vitiello, P.; Papa, A.; Calogero, A.; Sagnelli, C.; Casale, D.; Mottola, M.; Svanera, G.; Dodaro, C.A.; Martinelli, E.; Troiani, T.; Ciardiello, F.; Casale, B. Use of rituximab in NHL malt type pregnant in I° trimester for two times. *Open Med (Wars)*. 2019;14:757-760. DOI: 10.1515/med-2019-0087.

4. Sica, A.; Casale, B.; Spada, A.; Di Dato, M.T.; Sagnelli, C.; Calogero, A.; Buonavolontà, P.; Salzano, A.; Martinelli, E.; Saracco, E.; Troiani, T.; Dodaro, C.A.; Tammaro, D.; De Rimini, M.L.; Ciardiello, F.; Papa A. Differential diagnosis: retroperitoneal fibrosis and oncological diseases. *Open Med (Wars)*. In Press.

39. Fujita, H.; Nagatani, T.; Miyazawa, M.; et al. Primary cutaneous anaplastic large cell lymphoma successfully treated with low-dose oral methotrexate. *Eur J Dermatol*. 2008;18(3):360-361.

40. Yamane, N.; Kato, N.; Nishimura, M.; Ito, M.; Yanagi, T.; Osawa, R. Primary cutaneous CD30+ anaplastic large-cell lymphoma with generalized skin involvement and involvement of one peripheral lymph node, successfully treated with low-dose oral etoposide. *Clin Exp Dermatol*. 2009;34(5):e56-59.

41. Lee, W.J.; Moon, I.J.; Lee, S.H.; Won, C.H.; Chang, S.E.; Choi, J.H.; Moon, K.C.; Park, C.S.; Huh, J.; Lee, M.W. Cutaneous anaplastic large-cell lymphoma (ALCL): A comparative clinical feature and survival outcome analysis. *J Am Acad Dermatol*. 2016; 74 (6): 1135-43.

42. Martino, M.; Ciavarella S.; De Summa, S.; Russo, L.; Meliambro, N.; Imbalzano, L.; Gallo, G.A.; Moscato, T.; Messina, G.; Ferreri A.; Cuzzola, M.; Irrera, G.; Naso, V.; Cimminiello, M.; Console, G.; Loseto, G.; Tommasi, S.; Guarini, A. A Comparative Assessment of Quality of Life in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation Through an Outpatient and Inpatient Model. *Biol Blood Marrow Transplant*. 2018;24(3):608-613. DOI: 10.1016/j.bbmt.2017.09.021.

43. Calogero, A.; Sagnelli, C.; Carlomagno, N.; Tammaro, V.; Candida, M.; Vernillo, A.; Peluso, G.; Minieri, G.; Santangelo, M.; Dodaro, C.A.; et al. Familial polyposis coli: The management of desmoid tumor bleeding. *Open Med (Wars)*. 2019;14:572-576. DOI: 10.1515/med-2019-0064.

44. Ciavarella, S.; Minoia, C.; Quinto, A.M.; Oliva, S.; Carbonara, S.; Cormio, C.; Cox, M.C.; Bravo, E.; Santoro, F.; Napolitano, M.; Spina, M.; Loseto, G.; Guarini, A. Improving Provision of Care for Long-term Survivors of Lymphoma. *Clin Lymphoma Myeloma Leuk*. 2017;17(12):e1-e9. DOI: 10.1016/j.clml.2017.08.097.