Journal for ReAttach Therapy and Developmental Diversities
eISSN: 2589-7799
2022 December; 5 (2s): 249-257

Histological and Psychological Diagnosis Feature of Patients with Large Anaplastic Cells in Iraq

Sawsam Jaseim Al-Harbi[1*] Mariam Mohammed Burhan[2*] Hameda Abd Al-Mahdi Ghazi[3*] Ahmed Abdulkareem Nawres[4*]

[1,2] Department of Human Anatomy, College of Medicine, University of Babylon, Iraq
[3]Hammorabi Medical College, Anatomy and Histology Department, University of Babylon, Iraq
[4]Department of surgery , college of medicine , University of Babylon, Iraq
[*]Corresponding Author E-mail:drsawsamjasim@gmail.com

Received: 18-September-2022
Revised: 13-November-2022
Accepted: 18-December-2022

Abstract

The term (ALCL) refers to anaplastic large cell lymphoma, which is one of the most aggressive cancerous diseases, non-Hodgkin's lymphoma of cells (T-cell) that show pathological characteristics but differ genetically in the period from March to August (2021) The researchers found in the data base of the Hematology Department of Al-Amal Specialist Hospital in The Cancer Center in Baghdad Governorate reported on cases diagnosed with lymphoma The study included 10 biopsy samples from lymph nodes. All patients were males, with an average age ranging between 40-84 years. The study included other cases from another institution for the treatment of cancerous diseases, in addition to radiological procedures and pathological evaluation. The cases were diagnosed with this disease (ALCL) based on pathology, radiography, and clinical examination. Evidence of lymphadenopathy was present in all the cases involved in the research. All cases had a biopsy of the lymph nodes, most of the axillary nodes were localized, and most cases of swelling were of diffuse or moderate type. The results showed positive examination (CD30) for the sample and (ALK) and all patients had lymphadenopathy and all cases were positive for the examination (CD30) 100% and (ALK) 60 % while negative results 40% for (ALK) and (EMA) cases the majority in 20% and (EMA) the most common 40%. (ALCL) It is a lymphoma, cancerous, widespread and predatory, and there are effective therapeutic measures that reduce the toxicity of the patient in general. The type of lymphoid cells shows the extent of the spread of the disease and determines its type and severity, as the rays CT-SCAN show in order to determine the disease and its degree. Geographical area, race, age, gender and most of the cases were white with white skin that may be due to genetic factors or genetic mutations because they are more predisposed to mutations. The disease can be diagnosed by an experienced hematologist, but immunologically determined by factors or a group of immunological analyzes that were performed on the patient, and in conclusion(ALCL) considers highly virulent and predatory lymphomas and their early diagnosis is one of the important steps. Multiple cases of disease spread have been found to increase the ability to differentiate between groups of lymphocytes sub-groups (T cell) in order to better classify the sub-characteristics

Keywords: Treatment; Psychological effect; disease; aggressive cancerous diseases

Introduction

Lymphoma ALCL was defined in 1985 by Stein *et al* as acancerous disease with large cells indicated by the antibody Ki-1 produced against cancer cells(Hapgood and Savage,2015). In 1988 the disease was defined by a special classification called classification Kiel, is a highly virulent anaplastic large cell lymphoma LCA, which is a type of serious and rare cell carcinoma T-cell or B-cell and the term ALCL is used to describe the large cancerous diseases of the lymphoid glands because LCA is often combined with common white antigens, which is abbreviated LCA(Leventaki *et al*.,2020) . But in 1994 the disease was classified as a phenotype ALCLas a separate entity of lymphomas, while T-cell was classified with type B-cell as lymphomas B, the WHO indicated the possibilityALK positively,ALK negatively constitute a basic structure of the disease itself and another classification between that ALCLThey are positive and negative as a separate entity(Prieto-Torres *et al*.,2019) . In 2017, anaplastic lymphomas were classified as cancerous diseases and divided into multiple

divisions because there is a mistake between the term LCA(leukocyte common antigen-cells with ill-defined borders and they commonly exhibit several epithelial markers in lymphoma disease (Ventura *et al*.,2017) (Tsuyama *et al*.,2017). At the present time, studies have relied on the classification of the World Health Organization on the division of the disease and according to a group of complementary immune fraud. The disease is placed and then it was classified ALCL-ALK positively- ALCL-ALK-negatively **(** Collett *et al*.,2019 **)**. The phenotypes of the disease were classified as diffuse lymphomas B-cell , which are cancerous and aggressive tumors, and the World Health Organization has shown that (ALCL) is divided into (KLA positive) (ALK-negative) as a separate entityIn 2018, lymphomas were classified as separate cancers , while in 2001 it was based on the classification (REAL), which was based on an international classification ICD-3-5 and became an international gold standard for the classification of cancerous tumors. It was found that the cancer cells contain unusual cells with many cytoplasmic pockets(Al-Hamadani *et al*.,2015). It is a type of cancer, and it is a rare and aggressive form of tumor that represents an abnormal growth of B or T cells. Lymphoma arises in the lymph nodes and the invasion is internal and a kind of external invasion may occur when other organs are infected with cancer.And the lymph nodes were diagnosed as anaplastic or non-lymphocytic cancer and it led to the proliferation of activated cells T-cell and others that led to cell death(Whiteley *et al*.,2021). Also, CD30 was adopted in the classification of this disease through signals through CD30 in cases of anaplastic lymphomas**(** Cavalcanti *et al*.,2021 **)**. The disease is diagnosed in people aged 40 to 65, but it affects different ages and is more common in men than women. Gene abnormalities can affect the disease in addition to Other factors such as lifestyle, nutrition, smoking, and alcohol intake all affect the disease and do not achieve the goals of treatment(Wang *et al*.,2012). Lymphoma poses a great challenge. Despite all the possibilities of measures and prevention, the rates of infection are constantly increasing, and the increase may be due to environmental changes, genetic and other genetic changes, and some of them are viral. Assessment of topical clinical and pathological features of lymphoma in patients diagnosed with lymphoma on the basis of morphology and recently**(** Nam *et al*.,2021).introduced immunohistochemistry. The trends notice in the resulting data are likely to inform clinicians, researchers, and healthcare officials on which areas to focus on in their interventions (Abdulla *et al* .,2020).

The Aim of the Study

This study aimed to investigate more about prognosis of lymphoma cancers and its diagnostic tests.

Ethical Approval:

Valid consent was obtained from patients prior to their inclusion in the report. Before any samples were taken, each patient was informed of their right to accept or decline to participate in the research

Excluded samples

Samples were excluded in the event that the result of the histological examination was negative, the immunological analyzes represented by (CD30,ALK) were not performed for them.

Materials and Methodes

This study had 10 biopsy samples from lymph nodes. All of the patients were men, and they were all between the ages of 40 to 83 years in the department of Hematology at The Al-Amal Specialized Hospital in Baghdad province's Cancer Center from March to August 2021. The disease was diagnosed by taking a biopsy of the swollen glands, and the disease was classified according to the criteria of the World Health Organization, and any undiagnosed patient was excluded through biopsy.When researchers looked at the database of the department of Hematology of Hospital, they looked for people who had ALCL. This study also looked at cases from partner institutions, as well as radiology and pathology. Pathology, radiography, CT chest pictures and clinical examination were all used to make sure that the cases of ALCL were confirmed. All ALCL patients had signs of lymph node enlargement, which led to a biopsy of their lymph nodes. Because the most common sign of ALCL is swollen lymph nodes that are filled with fluid, a cytological examination of the outflow around the embed is needed to make a correct diagnosis. The first thing to do is to centrifuge and filter crisp, unfixed outflux fluid to manufacture air-dried smears stained with Wright-Giemsa stains. Prepare the cell mass so that hematoxylin and (eosin-stained with hematoxylin and eosin, cell nuclei are blue-purple and extracellular matter

is pink. compound: Hematoxylin, also known as natural blacks, is a type of hematoxylin or hematoxylin extracted from the heartwood of the logwood tree with a chemical formula Dye: It has been used as a histological stain, an ink, and as a dye for immunohistochemical investigation of formalin-fixed, paraffin-embedded histological parts. Fixation and mapping of the capsular amputation specimen are recommended to selects

multiple characteristic sections to see if microglia and the capsular tissue have been attack by them. Fine-needle aspiration isn't the best way to check for lymph node involvement, because it's more likely to show up only in a few places.

Histologic	CD30	EMA+cases	ALK
Common (classic) type	Positive	Majority	Positive
Giant cell-rich	Positive	Minority	Negative
Small cell	Positive	Most	Positive
Lymphohistiocytic	Positive	Most	Positive
Hodgkin-like	Positive	Minority	Negative
Sarcomatoid	Positive	Most	Positive
Small cell	Positive	Minority	Negative
Eosinophil rich	Positive	Minority	Negative
Neutrophil rich	Positive	Most	Positive
Signet ring	Positive	Majority	Positive

Table(1) :Histologic of ALCL and their correlation with immunophenotype.

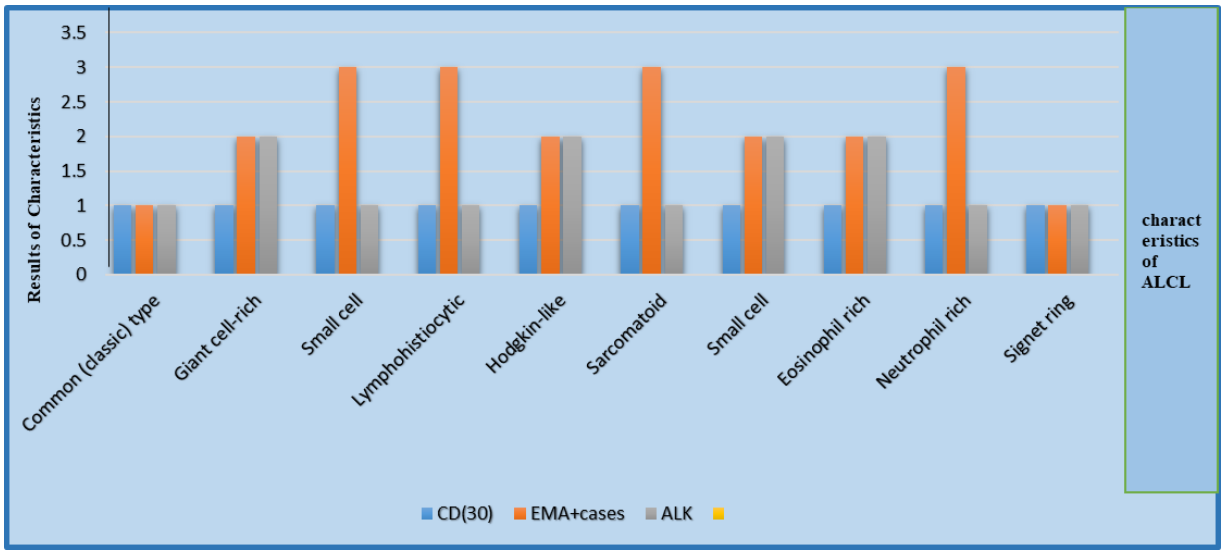
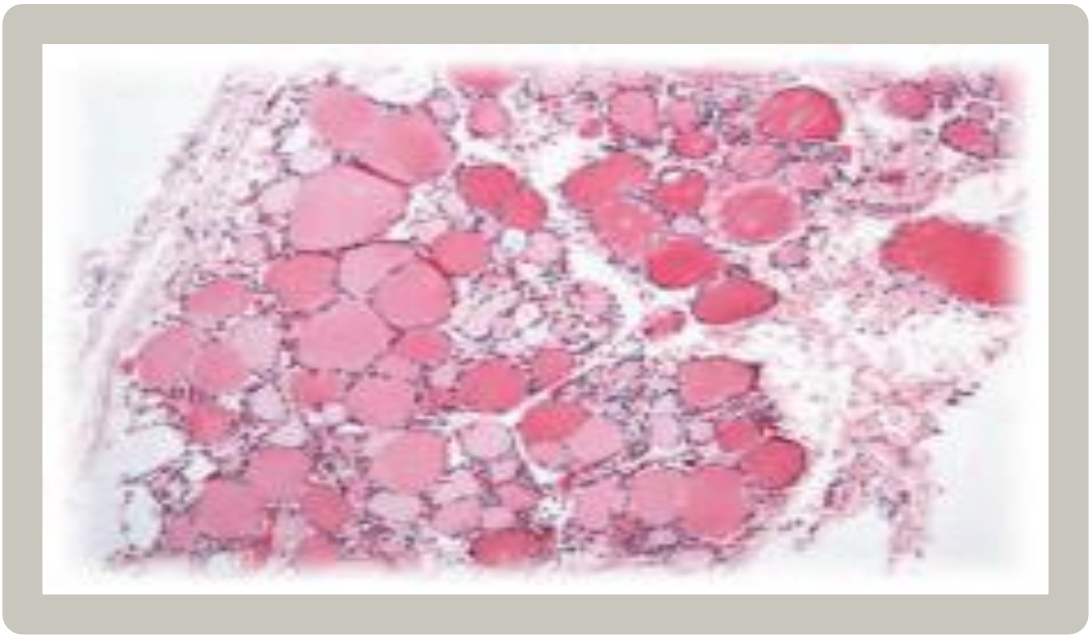


Figure (1):Correlation of immunophenotype with ALCL in patients



Figure(2):ALCL in a thyroid gland With HE stain

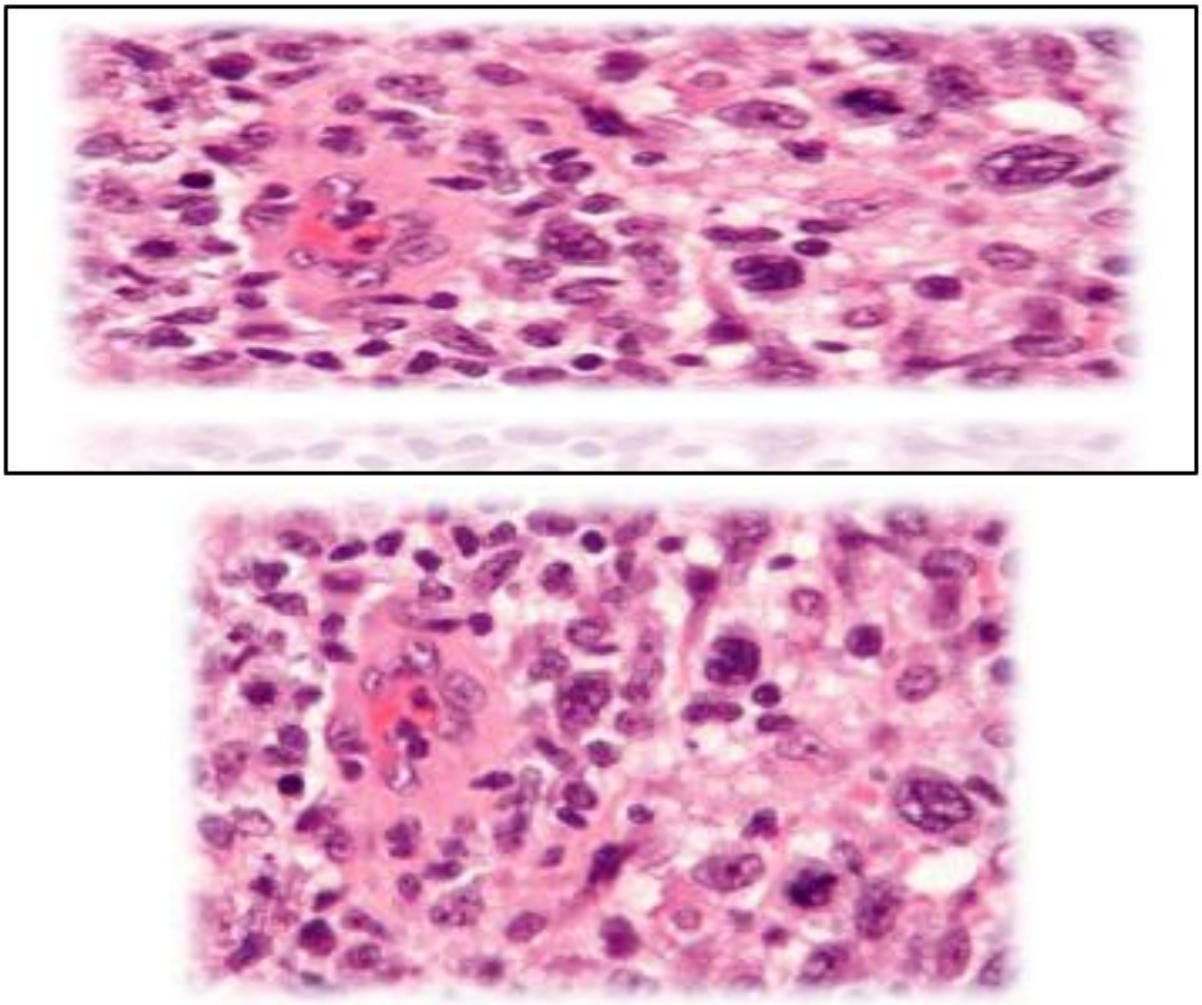
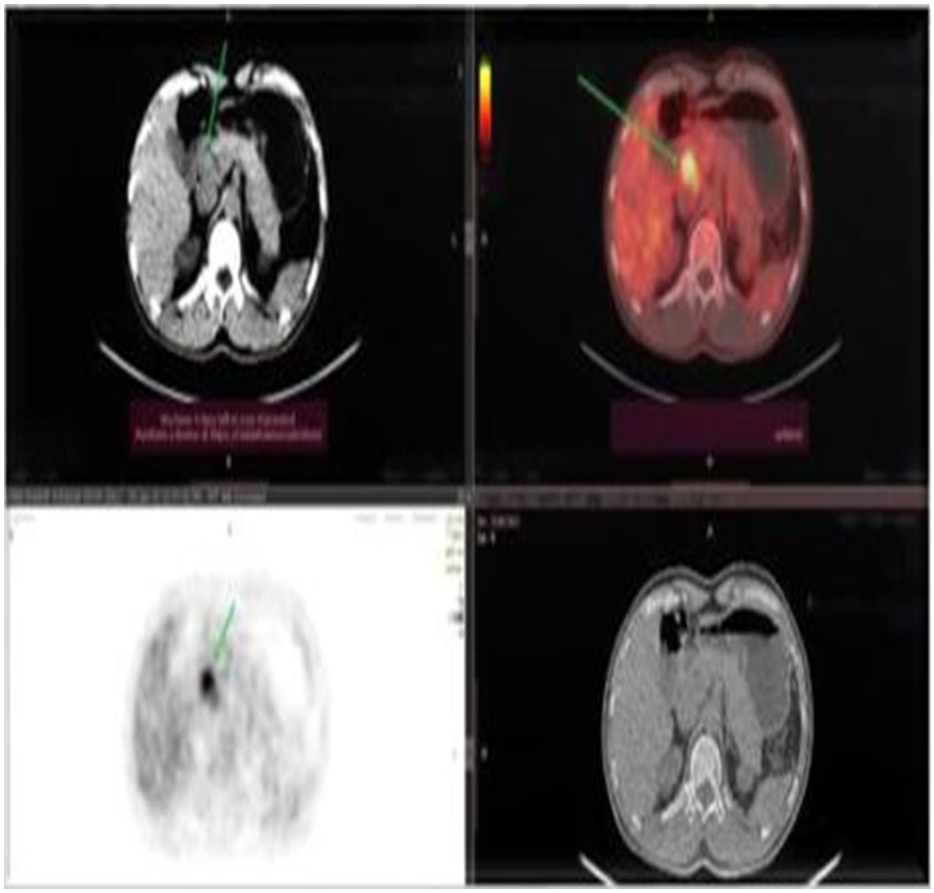


Figure (3): Normal Thyroid tissue,With HE stain



Figure(4):Anaplastic Large Cell LymphomaCT-SCAN/Thyroidgland

RESULTS and DISCUSION

The study included 10 people infected with ALCL, as shown in figure (1), and most of them were males and their ages ranged from 40-83 years, and had enlarged lymph nodes. Patients had positive results for CD30 at about 100% while ALK-positive results in 60% and negative results 40%, and EMA cases majority in 20% while(EMA minority and most)in 40%. This study agreement with the study of stein et al., 2000 and the study of (Jones *et al*.,2019) And another study by(Medeiros *et al*., 2007) showed agreement with the results from this study. A study by (Irshaid *et al*.,2020) showed another result similar to the results of this study. And (Kong *et al*.,2020) agree with this study, and studies by(Shimony *et al*.,2019) agree with this study. This study included pathological characteristics and immunological and molecular patterns for 10 cases with ALCL (T-cell lymphomas). Often the diagnosis of these diseases is the main trigger for the disease, as the T cells were initially found to be small to medium in size in most cases. They were classified as cases are anaplastic cell lymphoma positive for ALk, CD30. And all cases showed positive for CD30 while EMB was variable in cases. All results showed in Figure(1): Correlation of immunophenotype with ALCL, A helpful property was important perivascular infiltration; perivascular strikes an ordinary distinctive attribute or aspect of something. safety features like dual airbags. characteristic among both primary B- cell and T-cell lymphomas. Additionally, necrosis was seen in a significant grist of cases. In contrast, eosinophils and neutrophils were nonattending while plasma cells were copious, when present, these would favor an inflammatory process. Furthermore, in figure(2) a thyroid gland in ALCL With HE stain, the nuclei of the cell stained blue-purple and the material of the cell stained pink similar in a study by (Toda *et al*.,2014), while in figure(3)Normal Thyroid tissue, With HE stain, notice the thyroid follicles that have a rough surface like an underinflated beach ball and scant stromal material. From the other side, we notice in the image of the tumor the part of the large anaplastic cells as shown in the picture above from Figure(4)the CT-SCAN for the thyroid gland. Morphologic features of ALCL described The growth pattern is visible in partially involved lymph nodes, ALCL's histologic appearance was originally defined as a preferential paracortical involvement of lymph nodes with thyroid spread(Venkatraman *et al*.,2020). The application of newly developed immunophenotypic and molecular methods to the study of

hematolymphoid neoplasms. The patient needs a prior evaluation of his condition.They are required for diagnosis CD30and ALK are also therapeutic targets for the disease (Schwock *et al.*,2018). It includes modern strategies for diagnosing the disease and the use of modern and complex drugs for the necessity of cell survival. Point inhibitors work by preventing proteins from binding to other proteins and have been recognized by the Food and Drug Organization (Kong *et al*.,2021). ALCL varies markedly by geographic region, race, age, and sex. Most ALCL cases have been diagnosed in white populations. There is a large variation in the incidence of lymphoma type T-cell between (B-cell-NK cells) This discrepancy is due to genetic and ethnic factors, as well as environmental factors(Adams *et al*.,2016). The application of newly developed immunophenotypic and molecular methods to the study of hematolymphoid neoplasms. Patients diagnosed with ALCL require pretreatment evaluation. CD30 and ALK are required for accurate diagnosis and subclassification, and also serve as therapeutic targets in ALCL. Strategies to improve outcomes in ALCL include the design of next-generation drugs and the use of combined therapies that simultaneously target multiple nodes essential for cell survival. Immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins and have been approved by the FDA for a variety of cancer types. ALCL varies markedly by geographic region, race, age, and sex. Most ALCL cases have been diagnosed in white populations. Morphologic features of ALCL described The growth pattern is visible in partially involved lymph nodes, ALCL's histologic appearance was originally defined as a preferential paracortical involvement of lymph nodes with thyroid spread. The application of newly developed immunophenotypic and molecular methods to the study of hematolymphoid neoplasmsImmunological analyzes represented by CD30,ALK are performed for all patients .ALCL and it is a final check of the diseased condition. These analyzes are considered a final goal to reach an accurate diagnosis of the condition ALCL,Recent research has touched on finding a way to develop special treatments .through the design of new drugs and the use of special combinations of drugs that aim to keep the cell alive(Brown *et al*.,2019).

Conclusion

The disease ALCLis determined by a hematologist, but the immunophenotype is necessary, as the disease ALCL has been considered an immunological and highly virulent lymphoblastic disease, and it is also necessary to identify T- or B-cell groups for sub-classifications, for example, gene expression ofCD30And the loss of T-cell codes, but the molecular characteristics of the disease ALCL and the mechanism of tumor occurrence, the disease ALCL were considered an important feature for diagnosis, and for more than years, many studies have been identifying the disease on the basis of ALK It gives the diagnostic characteristics of the disease. The heterogeneity of the disease was determined by the prominent characteristics of the disease and by specific clinical characteristics of the disease, but there is an urgent need for more studies and research for the purpose of understanding the mechanism of disease action and finding a rapid diagnostic attempt for the disease. The study indicates that the basic diagnosis of CD30 For all lymphomas allows, rapid identification of the disease, and the primary purpose of all cellular annotations of tumors was to give a strong idea to the diagnosis There is still an urgent need for practical research linking data, imaging, laboratory, and molecular cells to determine the causes of cancerous tumors and to develop and find rapid methods for diagnosing and controlling the disease. From what was mentioned above, we find that there is a higher prevalence of the disease among males than females, and the younger one is more prevalent, and this may be due to genetic and hormonal factors. In addition to the rapid diagnostic methods that make the diagnosis and detection of the disease a means to identify, reduce and control the spread of the disease. It is a rare and predatory disease characterized by positive neoplastic cells, and there are strong pathological guidelines for diagnosis, in addition to the diagnosis of a hematologist.

References

[1]. Abdulla, F.R., Zhang, W., Wu, X., Honda, K., Qin, H., Cho, H., Querfeld, C., Zain, J., Rosen, S.T., Chan, W.C. and Parekh, V., (2020). Genomic Analysis of Cutaneous CD30-Positive Lymphoproliferative Disorders. *JID innovations*, *2*(1), p.100068.

[2]. Adams, S.V., Newcomb, P.A. and Shustov, A.R., (2016). Racial patterns of peripheral T-cell lymphoma incidence and survival in the United States. *Journal of Clinical Oncology*, *34*(9), p.963.

[3]. Advani, R.H., Ansell, S.M., Lechowicz, M.J. *et al*. (2016). A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) alternating with Pralatrexate (P) as front line therapy for

patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial. Br J Haematol 172 (4): 535-544.

[4]. Alam, M.W., (2021). Investigating ALK inhibitors alone or in combination as therapeutic options for ALK-positive neuroblastoma.

[5]. Al-Hamadani, M., Habermann, T.M., Cerhan, J.R. *et al*. (2015). Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol 90 (9): 790795

[6]. Al-Hamadani, M., Habermann, T.M., Cerhan, J.R. *et al*. (2015). Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol 90 (9): 790795.

[7]. Anderson JR, Armitage JO, Weisenburger DD.(2019). Epidemiology of the non-Hodgkin's lymphomas: Distributions of the major subtypes differ by geographic

[8]. Brown, ization and anaplastic large cell lymphoma .AT., Harvie, F. and Stewart, S., (2019). A different perspective on breast implant surface texturLCL). *Aesthetic Surgery Journal*, *39*(1), pp.56-63.

[9]. Cavalcanti, I.D.L. and Soares, J.C.S., (2021). *Advances in Cancer Treatment: From Systemic Chemotherapy to Targeted Therapy*. Springer Nature.

[10]. Collett, D.J., Rakhorst, H., Lennox, P., Magnusson, M., Cooter, R. and Deva, A.K., (2019). Current risk estimate of breast implant–associated anaplastic large cell lymphoma in textured breast implants. *Plastic and reconstructive surgery*, *143*(3S), pp.30S-40S.

[11]. DePaola, N.E.K. and Coggins, H. (2019). Breast implantassociated anaplastic large cell lymphoma: what we know. J Adv Pract Oncol 10 (1): 54-61.

[12]. Di Raimondo, C., Parekh, V., Song, J.Y., Rosen, S.T., Querfeld, C., Zain, J., Martinez, X.U. and disorders. *International Scholarly Research Notices*, (2011).double-blind, randomised, phase 3 trial. *The Lancet*, 393(10168), pp.229-240.

[13]. Ducray, S.P., Natarajan, K., Garland, G.D. *et al*. (2019). The transcriptional roles of ALK fusion proteins in tumorigenesis. Cancers (Basel) 11 (8): 1074

[14]. Ducray, S.P., Natarajan, K., Garland, G.D. *et al*. (2019). The transcriptional roles of ALK fusion proteins in tumorigenesis. Cancers (Basel) 11 (8): 1074

[15]. Fetica, B., Achimas-Cadariu, P., Pop, B., Dima, D., Petrov, L., Perry, A.M., Nathwani, B.N., Müller-Hermelink, H.K., Diebold, J., MacLennan, K.A. and Fulop, A., (2017). Non- Hodgkin lymphoma in Romania: a single-centre experience. *Hematological Oncology*, *35*(2), pp.198-205.

[16]. Gascoyne, R.D., Aoun, P., Wu, D., Chhanabhai, M., Skinnider, B.F., Greiner, T.C., Morris, S.W., Connors, J.M., Vose, J.M., Viswanatha, D.S.

[17]. Guru Murthy, G.S., Hamadani, M., Bhatt, V.R. *et al.* (2017). Systemic anaplastic lymphoma kinasepositive anaplastic large cell lymphoma: a population-based analysis of incidence and survival. Clin Lymphoma Myeloma Leuk 17 (4): 201-206 Hapgood, G. and Savage, K.J., (2015). The biology and management of systemic anaplastic larg cell lymphoma. *Blood, The Journal of the American Society of Hematology*,

[18]. Horwitz, S., O'Connor, O.A., Pro, B., Illidge, T., Fanale, M., Advani, R., Bartlett, N.L., Christensen, J.H., Morschhauser, F., Domingo-Domenech, E. and Rossi, G., (2019). Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global,https://doi.org/10.1002/ pbc.26902

[19]. Hu, S.; Xu-Monette, Z.Y.; Balasubramanyam, A.; Manyam, G.C.; Visco, C.; Tzankov, A.; Liu, W.M.; Miranda, R.N.; Zhang, L.; Montes-Moreno, S.; *et al*. CD30 expression defines a novel subgroup of diffuse large B-cell lymphoma with favorable prognosis and distinct gene expression signature: A report from the International DLBCL Rituximab- CHOP Consortium Program Study. Blood(2013), *121*, 2715-2724

[20]. Irshaid, L. and Xu, M.L., (2020). ALCL by any other name: the many facets of anaplastic large cell lymphoma. *Pathology*, 52(1), pp.100-110.

[21]. Javanmardi, N., (2017). *Genomic instability and genetic heterogeneity in neuroblastoma tumours.*journal of clinical pathology, *127(5), pp.707-722.*

[22]. Kim, B., Roth, C., Young, V.L., Chung, K.C., van Busum, K., Schnyer, C. and Mattke, S., (2011). Anaplastic large cell lymphoma and breast implants: results from a structured expert consultation process. *Plastic and reconstructive surgery*, 128(3), pp.629-639.

[23]. King, R.L., Dao, L.N., McPhail, E.D., Jaffe, E.S., Said, J., Swerdlow, S.H., Sattler, C.A., Ketterling, R.P., Sidhu, J.S., Hsi, E.D. and Karikehalli, S., (2016). Morphologic features of ALK-negative anaplastic large cell lymphomas with DUSP22 rearrangements. *The American journal of surgical pathology*, 40(1), p.36.

[24]. Kong, J. and Feldman, A.L., (2021). The Spectrum of Anaplastic Large-cell Lymphoma. *The Peripheral T-Cell Lymphomas*, pp.129-144.

[25]. Kong, J., Dasari, S., and Feldman, A.L. (2020). PD-L1 expression in anaplastic large cell lymphoma. Mod Pathol 33 (6): 1232-1233.

[26]. Lamant, L., McCarthy, K., d'Amore, E., Klapper, W., Nakagawa, A., Fraga, M., Maldyk, J., Simonitsch-Klupp, I., Oschlies, I., Delsol, G. and Mauguen, A., (2011). Prognostic impact of morphologic and phenotypic features of childhood ALK-positive anaplastic large-cell lymphoma: results of the ALCL99 study. *Journal of Clinical Oncology*, 29(35), pp.4669-4676.

[27]. Laurent C, Do C, Gourraud PA, de Paiva GR, Valmary S, Brousset P. Prevalence of common non-Hodgkin lymphomas and subtypes of Hodgkin lymphoma by nodal site of involvement: A systematic retrospective review of 938 cases. Medicine (Baltimore) (2015);94:e98

[28]. Leoncini L, Del Vecchio M T, Kraft R, Megha T, Barbini P, *etal.:* Hodgkin's disease and CD30positive anaplastic large cell lymphomas--a continuous spectrum of malignant disorders. A quantitative morphometric and immunohistologic study. Am J Pathol 137: 1047-1057, (1990).

[29]. Leventaki, V., Bhattacharyya, S. and Lim, M.S., (2020). January. Pathology and genetics of anaplastic large cell lymphoma. In Seminars in diagnostic pathology (Vol. 37, No. 1, pp. 57-71). WB Saunders.

[30]. Masoumipour, M., Abbaspanah, B. and Mousavi, S.H., 2021. Extracellular vesicles: Regenerative medicine prospect in hematological malignancies. *Cell Biology International*, 45(10), pp.2031-2044.

[31]. McClain, K.L., Bigenwald, C., Collin, M., Haroche, J., Marsh, R.A., Merad, M., Picarsic, J., Ribeiro, K.B. and Allen, C.E.,(2021). Histiocytic disorders. *Nature Reviews Disease Primers*, 7(1), pp.1-26

[32]. Medeiros, L.J. and Elenitoba-Johnson, K.S., (2007). Anaplastic large cell lymphoma. *American journal of clinical pathology*, *127*(5), pp.707-722.

[33]. Nam, S.Y., Zhang, X., Faruq, O., Chien, P.N., Dönmez, N. and Heo, C.Y., (2021). An Impact of Different Silicone Breast Implants on the Bacterial Attachment and Growth. *Journal of Biomaterials and Nanobiotechnology*, *12*(3), pp.21-33.

[34]. Ninkovic S, Lambert J. Non hodgkin lymphoma. Medicine 2017;45:297-304.

[35]. Paes FM, Kalkanis DG, Sideras PA, Serafini AN. FDG PET/CT of extranodal involvement in non-Hodgkin lymphoma and Hodgkin disease. Radiographics (2010);30:269-9

[36]. Pan, Z., Hu, S., Li, M., Zhou, Y., Kim, Y.S., Reddy, V., Sanmann, J.N., Smith, L.M., Chen, M., Gao, Z. and Wang, H.Y.,(2017). ALK-positive large b-cell lymphoma. *The American journal of surgical pathology*, 41(1), pp.25-38.

[37]. Parrilla Castellar, E.R., Jaffe, E.S., Said, J.W., Swerdlow, S.H., Ketterling, R.P., Knudson, R.A., Sidhu, J.S., Hsi, E.D., Karikehalli, S., Jiang, L. and Vasmatzis, G., (2014). ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood, The Journal of the American Society of Hematology*, 124(9), pp.1473-1480.

[38]. Perera, L.P., Zhang, M., Nakagawa, M. *et al.(* 2017). Chimeric antigen receptor modified T cells that target chemokine receptor CCR4 as a therapeutic modality for T-cell malignancies. Am J Hematol 92 (9): 892-901

[39]. Pletneva, M.A. and Smith, L.B., (2014). Anaplastic large cell lymphoma: features presenting diagnostic challenges. *Archives of Pathology and Laboratory Medicine*, 138(10), pp.1290-1294.

[40]. Ratner, L., Waldmann, T.A., Janakiram, M., and Brammer, J.E. (2018). Rapid progression of adult T-cell leukemia-lymphoma after PD-1 inhibitor therapy. N Engl J Med 3

[41]. Redaelli, S., Ceccon, M., Antolini, L. *et al*. (2016). Synergistic activity of ALK and mTOR inhibitors for the treatment of NPM-ALK positive lymphoma. Oncotarget 7 (45): 72886-72897.

[42]. review. *Current Hematologic Malignancy Reports*, 15(4), pp.333-342.

[43]. Rigaud, C., Abbou, S., Minard-Colin, V. *et al*. (2018). Efficacy of nivolumab in a patient with systemic refractory ALK+ anaplastic large cell lymphoma. Pediatr Blood Cancer 65(4)

[44]. Schwock, J., Quest, G.R. and Geddie, W.R., (2018). Molecular Applications in Hematolymphoid Cytology. In *Molecular Applications in Cytology* (pp. 151-177). Springer, Cham.

[45]. Shimony, S., Horowitz, N., Ribakovsky, E. et al. (2019). Romidepsin treatment for relapsed or refractory peripheral and cutaneous T-cell lymphoma - real-life data from a national multicenter observational study. Hematol Oncol 37 (5): 569-577.

[46]. Shustov, A. and Soma, L. (2017). Anaplastic large cell lymphoma: contemporary concepts and optimal management. Cancer Treat Res 176: 127-144.

[47]. Stein, H., Foss, H.D., Durkop, H., Marafioti, T., Delsol, G., Pulford, K., Pileri, S. and Falini, B., (2000). CD30+ anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood, The Journal of the American Society of Hematology*, 96(12), pp.3681-3695.

[48]. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein, H, Siebert R, *et al*. (2016) .The revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-9

[49]. Swerdlow, S., Campo, E., Harris, N. *et al.* (2017). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, (rev. 4ed). Lyon: International Agency for Research on Cancer

[50]. Tajima K, Hinuma Y: Epidemiology of HTLV-I/II in Japan and the world. Gann Monogr Canc Res 39:129-149, (1992).

[51]. Toda, S., Aoki, S., Uchihashi, K., Matsunobu, A., Yamamoto, M., Ootani, A., Yamasaki, F., Koike, E. and Sugihara, H., (2011). Culture models for studying thyroid biology and

[52]. Koike, E. and Sugihara, H., (2011). Culture models for studying thyroid biology and disorders. *International Scholarly Research Notices*, *2011*.

[53]. Tsuyama, N., Sakamoto, K., Sakata, S., Dobashi, A. and Takeuchi, K., (2017). Anaplastic large cell lymphoma: pathology, genetics, and clinical aspects. Journal of clinical and experimental hematopathology, 57(3), pp.120-142.

[54]. Turner, S.D., Inghirami, G., Miranda, R.N., and Kadin, M.E. (2019). Cell of origin and immunologic events in the pathogenesis of breast implant-associated anaplastic large-cell lymphoma. Am J Pathol 190 (1): 2-10.

[55]. Vassallo, J.; Lamant, L.; Brugieres, L.; Gaillard, F.; Campo, E.; Brousset, P.; Delsol, G. ALK-positive anaplastic large cell lymphoma mimicking nodular sclerosis Hodgkin's lymphoma: Report of 10 cases. *Am. J. Surg. Pathol.* (2006), *30*, 223-229

[56]. Venkatraman, L., 2020. Nodal Malignant Lymphoma (With Comments on Extranodal Malignant Lymphoma and Metastatic Cancer). In *Histopathology Reporting* (pp. 427-447). Springer, Cham.

[57]. Whiteley, A.E., Price, T.T., Cantelli, G. and Sipkins, D.A., (2021). Leukaemia: A model metastatic disease. *Nature Reviews Cancer*, *21*(7), pp.461-475.

[58]. Wu, J., Fu, J., Zhang, M., and Liu, D. (2015). AFM13: a first-in-class tetravalent bispecific anti-CD30/CD16A antibody for NK cell-mediated immunotherapy. J Hematol Oncol 8: 96 Yabe, M. and Medeiros, L.J., (2018). Pathology of Non-Hodgkin and Hodgkin Lymphomas. In *Neoplastic Diseases of the Blood* (pp. 773-826). Springer, Cham.

[59]. Prieto-Torres, L., Rodriguez-Pinilla, S.M., Onaindia, A., Ara, M., Requena, L. and Piris, M.Á., (2019). CD30-positive primary cutaneous lymphoproliferative disorders: molecular alterations and targeted therapies. *haematologica*, *104*(2), p.226.

[60]. Ventura, L., Gnetti, L., Silini, E.M., Rindi, G., Carbognani, P., Rusca, M. and Ampollini, L., 2017. Primary atypical carcinoid tumor of the mediastinum: a very rare finding. *Journal of thoracic disease*, *9*(4), p.E367.

[61]. Wang, Y.F., Yang, Y.L., Gao, Z.F., Zhou, C.J., Gregg, X., Shi, Y.F., Wang, J., Yang, X.F. and Ke, X.Y., (2012). Clinical and laboratory characteristics of systemic anaplastic large cell lymphoma in Chinese patients. *Journal of Hematology & Oncology*, *5*(1), pp.1-9.

[62]. Jones, J.L., Hanby, A.M., Wells, C., Calaminici, M., Johnson, L., Turton, P., Deb, R., Provenzano, E., Shaaban, A., Ellis, I.O. and Pinder, S.E., (2019). Breast implant- associated anaplastic large cell lymphoma (BIA-ALCL): an overview of presentation and pathogenesis and guidelines for pathological diagnosis and management. *Histopathology*, *75*(6), pp.787-796.