Cancer Association of South Africa (CANSA)

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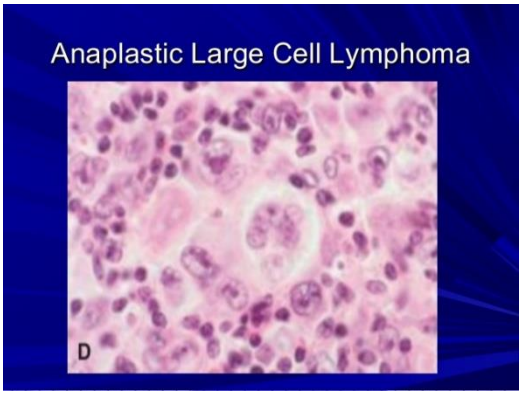
Fact Sheet
on
Anaplastic Large Cell Lymphoma

Introduction

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL), and one of the subtypes of T-cell lymphoma. ALCL comprises about one percent of all NHLs and approximately 16 percent of all T-cell lymphomas.



Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL). It is more common in children and young adults.

ALCL develops when white blood cells called T-cells become abnormal. These usually build up in the lymph nodes, but can affect other parts of the body.

There are two types of ALCL, a type that affects mainly the skin (cutaneous ALCL) and a type that affects other body organs (systemic ALCL). Systemic ALCL also has two types, ALK-positive (anaplastic lymphoma kinase) and ALK-negative. ALK-positive ALCL occurs more often in children and young adults. ALK-negative ALCL tends to occur in older adults. Systemic anaplastic large cell lymphoma (ALCL) is an aggressive $CD30^{+}$ non-Hodgkin lymphoma.

Primary cutaneous ALCL presents in older age groups (median age 55 years), and is rare in children. It is 2-3 times more common in men than in women. Systemic ALK-positive ALCL is more likely to affect children and young adults (median age 34), although there is a group who present later in life. People with systemic ALK-negative ALCL present at a later age (median age 58 years). Systemic ALCL is slightly more common in men than in women.

Incidence of Anaplastic Large Cell Lymphoma

The outdated National Cancer Registry (2016) does not provide information regarding Anaplastic Large Cell Lymphoma (ALCL).

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Causes and Risk Factors for Anaplastic Large Cell Lymphoma

The causes of ALCL are mostly unknown. Like other cancers, it is not infectious and cannot be passed on to other people. It is more likely to affect children and young adults, and it is more common in males than females.

Very rarely, breast implants are linked to ALCL. The lymphoma often only affects the area around the breast implant and is treated with surgery.

Gerbe, A., Alame, M., Dereure, O., Gonzalez, S., Durand, L., Tempier, A., De Oliveira, L., Tourneret, A., Costes-Martineau, V., Cacheux, V. & Szablewski, V. 2019.

"Despite distinct clinical presentation and outcome, systemic, primary cutaneous, and breast implant-associated anaplastic large cell lymphomas (S-, PC-, BI-ALCL) ALK-negative (ALK-) show similar histopathological features including the presence of the "hallmark" cells with horseshoe-shaped nuclei and CD30 protein expression. The purpose was to better characterize these three entities using immunohistochemistry and FISH (Fluorescent in situ hybridization) to identify biomarkers differently expressed and that might be involved in their pathogenesis. Twenty-two S-ALCL ALK-, 13 PC-ALCL, and 2 BI-ALCL were included. Cases were tested for P53, P63, MUM1, MYC, GATA3, p-STAT3, PD1, and PDL1 protein expression and DUP22, TP53, TP63, MYC, and PDL1 chromosomal aberrations. As expected, S-ALCL ALK- patients had adverse outcome compare to PC and BI-ALCL. No difference was observed between the three groups concerning protein expression except for MUM1 that was significantly more frequently expressed in S-ALCL ALK- compared to PC-ALCL. In particular, constitutive activation of the STAT3 pathway and PDL1/PD1 immune-checkpoint expression was present in the three entities. TP53 deletion and PDL1 gene amplification were the commonest cytogenetic alterations and were present in the three entities. None of the studied biological parameters was associated with prognosis. Despite distinct clinical behavior, S-ALCL ALK-, PC-ALCL, and BI-ALCL share similar biological features. Larger series should be investigated with the current approach to determine more precisely the activity and the prognostic value of these biomarkers and pathways in each group."

Fitzal, F., TAurner, S.D. & Kenner, L. 2019.

"Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) may occur after reconstructive or aesthetic breast surgery. Worldwide, approximately 1.7 million breast implant surgeries are performed each year. To date, over 500 cases of BIA-ALCL have been reported around the world, with 16 women having died. This review highlights the most important facts surrounding BIA-ALCL. There is no consensus regarding the true incidence rate of BIA-ALCL as it varies between countries, is probably significantly under-reported and is difficult to estimate due to the true number of breast prostheses used largely being unknown. BIA-ALCL develops in the breast mostly as a seroma surrounding the implant, but contained within the fibrous capsule, or more rarely as a solid mass that can become invasive infiltrating the chest wall and muscle, in some instances spreading to adjacent lymph nodes, in these cases having a far worse prognosis. The causation of BIA-ALCL remains to be established, but it has been proposed that chronic infection and/or implant toxins may be involved. What is clear is that complete capsulectomy is required for treatment of BIA-ALCL, which for early-stage disease leads to cure, whereas chemotherapy is needed for advanced-stage disease, whereby improved results have been reported with the use of brentuximab. A worldwide database for BIA-ALCL and implants should be supported by local governments."

In many cases, experts don't know exactly what causes lymphoma. However, some things may in-crease the risk of developing it.

Other causes and risk factors may include:

- Infections
- Presence of auto-immune disease
  - Rheumatoid arthritis
  - Sjogren's syndrome - Sjogren's syndrome is an autoimmune disease. In Sjogren's syndrome, there is an attack on the glands that make tears and saliva. This causes a dry mouth and dry eyes.
  - Systemic lupus erythematosus
- Previous cancer
- Having a close relative with non-Hodgkin's Lymphoma

Signs and Symptoms of Anaplastic Large Cell Lymphoma

Usually, the first symptom may include a painless swelling in the neck, armpit or groin. General symptoms may include loss of appetite and tiredness. Some people may also have night sweats, high temperatures (fevers) or weight loss. Other symptoms depend on where the lymphoma is in the body.

Diagnosis of Anaplastic Large Cell Lymphoma

An excisional lymph node biopsy is preferred to make the diagnosis. A core needle biopsy may be acceptable as long as there is enough tissue for histology, flow cytometry, cytogenetics, and gene rearrangement studies. A fine needle aspirate is almost always inadequate to establish the diagnosis. Biopsy of skin lesions and/or a bone marrow biopsy can also help establish the diagnosis.

Useful laboratory tests include a complete blood count to assess for sequelae of bone marrow involvement, such as anaemia and thrombocytopenia.

Occasionally circulating lymphoma cells will be visible on peripheral blood smear.

An elevated LDH is suggestive of lymphoma and impacts prognosis. A normal LDH does not rule out lymphoma, nor does an elevated LDH conclusively establish the diagnosis.

HIV testing is important, since HIV is a risk factor for lymphoma and acute HIV infection can present with many of the same symptoms as ALCL, including fever, weight loss, and lymphadenopathy.

A comprehensive metabolic profile is important to assess for renal and liver impairment as a result of mechanical obstruction of the ureters and biliary ducts respectively, or from direct organ involvement with lymphoma. Impaired organ function can also affect chemotherapy selection and dosing. Hyperphosphatemia, hyperuricemia, hyperkalaemia, and/or renal impairment can suggest spontaneous tumour lysis syndrome from an aggressive ALCL.

Staging of Anaplastic Large Cell Lymphoma

Staging of Anaplastic Large Cell Lymphoma is important as it may assist in the design of a treatment plan. The stages are as follows:

- *Stage I*: Involvement of a single lymph node region or lymphatic structure;
- *Stage II*: Involvement of 2 or more lymph node regions on the same side of the diaphragm;

- *Stage III*: Involvement of lymph node regions or structures on both sides of the diaphragm;
- *Stage IV*: Involvement of extra-nodal sites beyond that proximal to the nodal site involved in Stage I-III.

Treatment of Anaplastic Large Cell Lymphoma

Systemic ALCL is treated with the chemotherapy regimen CHOP (cyclophosphamide, doxorubin, vincristine and prednisolone). Other therapies include radiotherapy, stem cell transplants and steroid therapy. People with ALK-positive ALCL generally respond well to chemotherapy. Primary cutaneous ALCL may go into spontaneous remission (the disease goes away without treatment). However this is inevitably followed by a relapse. If no spontaneous remission occurs, or if the lymphoma relapses, the most common treatments for this type of ALCL include radiation therapy and/or surgery to remove the affected area of skin. When there is extensive involvement that cannot be treated with these localised therapies, systemic chemotherapy may be required.

Because of disease rarity, there are currently no randomized controlled trials (RCTs) to guide treatment decisions in ALCL, and as a result, the optimal therapy remains unknown. The majority of evidence describing outcomes for adult patients with systemic ALCL and the impact of various treatment regimens comes from retrospective studies or subgroup analyses of completed prospective studies in aggressive lymphomas or PTCLs.

Van-de-Velde, V. & Zhou, Y. 2019.

"Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin lymphomas characterized by an infiltration of malignant monoclonal T lymphocytes into the skin. Mycosis fungoides (MF), the most common subtype, and the rarer Sézary syndrome (SS), are considered the classical forms of CTCL, which, because of a varying presentation and lack of genetic and immunophenotypical markers, can often have a delayed diagnosis. With skin-directed topical treatment being the mainstay of therapy in the early stages, there is an absence of long-term curative therapies for advanced disease. Recent insight into the pathogenesis of CTCL has identified new potential therapeutic targets including the monoclonal antibody therapies, brentuximab vedotin and mogamulizumab. Brentuximab vedotin, an anti-CD30 antibody-drug conjugate, received extended approval by the US FDA in 2017 to include primary cutaneous anaplastic large-cell lymphoma and CD30-expressing MF. Mogamulizumab, an anti-CCR4 antibody, received FDA approval in 2018 for relapsed or refractory MF and SS. Further targets and therapies continue to be investigated, including the monoclonal antibody therapy alemtuzumab, an anti-CD52 antibody, and the immune checkpoint blockade therapies, pembrolizumab and nivolumab. These new and emerging targets and therapies may lead to a promising broadening of CTCL treatment options in the future."

Resham, S., Khan, R., Ashraf, S., Rizvi, A. & Altaf, S. 2019.

BACKGROUND: Different approaches have been adopted in the treatment of anaplastic large cell lymphoma (ALCL); there is a lack of consensus with regard to standard treatment. Because of paucity of data from low and middle-income countries, we reviewed the clinical features and treatment outcomes of children with ALCL.

METHODS: All ALCL patients under 16 years of age diagnosed from 2005 to 2015 at Aga Khan University Hospital and The Indus Hospital were identified. Clinical features and treatment outcomes were analyzed.

RESULTS: Thirty-two (n=32) patients met the inclusion criteria. Cervical Lymphadenopathy was the most common presentation (34.3%, n=11). Advanced disease was seen in 68.7% (n=22) (stages III and IV). Fourteen (42.4%) were treated on ALCL-99, 30.3% (n=10) on multicenter protocol-842 regimen, 9% (n=3) on adriamycin-prednisolone-oncovin (doxorubicin, prednisone, vincristine) regimen, and 16% (n=5) were treatment abandonments. Five-year overall survival was 70.6% (95% confidence interval: 47.8%-84.9%), and

5-year event-free survival (EFS) considering treatment abandonment and death as an event was 52.3 % (95% confidence interval: 23.5%-74.8%).
CONCLUSIONS: Significant therapy-related mortality (27.7%) was observed. Treatment abandonment and therapy-related toxicity were the major barriers for better outcomes. However, less intensive outpatient regimens, such as adriamycin-prednisolone-oncovin regimen, may decrease the number of hospitalizations, hence reducing treatment abandonment in the low and middle-income country.

Yamashita, T., Higashi, M., Kawano, R., Momose, S., Tokuhira, M., Kzaki, M. & Tamaru, J.I. 2019.
"Anaplastic large cell lymphoma (ALCL) with TP63 rearrangement is a new entity and has the most dismal prognosis in all types of ALCL. This might be due to the resulting fusion protein having N-terminal truncated p63 with high oncogenic ability. Since this N-terminal domain has the function of tumor suppressor activity, the mechanism for high oncogenic capacity is thought to be the dominant negative function. Here, we report two ALCL cases with TP63 rearrangement that was each given too short a prognosis (Case 1 and 2: four and six months) in spite of intensive treatment. Immunohistochemically, p63 was highly expressed, and a sprit signal was detected using a TP63 break apart fluorescence in situ hybridization (FISH) in each case. Additionally, a poor prognostic marker of ALCL, all cytotoxic molecules (TIA-1, Granzyme B, and Perforin) were also expressed in almost all ALCL cells. Taken together, we suggest that not only the dominant negative function of N-truncated p63 but also the effect of cytotoxic molecules may influence the dismal prognosis of ALCL with TP63 rearrangement."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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