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Respiratory Failure by Anaplastic Large T Cell Lymphoma (ALCL) – A Literature Review About a Clinical Case Report.

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RESUMO

O Linfoma Anaplásico de Grandes Células T (LAGC), é um linfoma raro e agressivo de células T não Hodgkin. É uma entidade incluída no grupo de doenças linfoproliferativas CD30+. Representa cerca de 1–3% dos Linfomas Não Hodgkin (LNH) e cerca de 15% dos linfomas periféricos de células T a nível mundial.

Existem quatro subtipos de Linfoma Anaplásico de Grandes Células T de acordo com a Classificação de Tumores de Tecidos Hematopoiéticos e Linfoides da Organização Mundial de Saúde (OMS): 1) linfoma anaplásico quinase (ALK) sistémico positivo (ALK+LAGC); 2) ALK sistémico negativo (ALK- LAGC); 3) LAGC cutâneo primário (pc-LAGC); e 4) linfoma anaplásico associado ao implante mamário (BIA- LAGC). Estes quatro subtipos distinguem-se pelos seus sintomas clínicos, características genéticas, prognósticos e tratamento.

O seu crescimento sinusoidal e o padrão de distribuição perivascular inerente, que pode ser encontrado em aproximadamente 75% dos casos, gera uma infiltração linfomatosa (linfangite pulmonar), podendo resultar, consequentemente, numa Síndrome Respiratória Aguda Grave (SRAG), a qual poderá requerer ventilação mecânica.

De acordo com a literatura, apesar das contraindicações, doentes imunossuprimidos melhoram consideravelmente quando submetidos ao regime de Ciclofosfamida, Doxorrubicina, Vincristina e Prednisona (CHOP ou CHOP em combinação com Etoposido (CHOEP), tratamento padrão neste linfoma) e, simultaneamente, à ventilação mecânica. O suporte ventilatório é ponderado nestes doentes quando a envolvimento pulmonar é considerado reversível. Para que a ECMO (do inglês *Extracorporeal Membrane Oxygenation*) seja considerada como parte do tratamento, devem existir estratégias terapêuticas robustas e possivelmente eficazes que possam assegurar a reversibilidade da doença. Neste sentido, a ECMO funciona como “uma ponte” para a possibilidade de realização de quimioterapia que possa reverter as causas da falência orgânica que requerem a necessidade de ECMO e, desta forma, controlar a doença em causa.

Neste *Case Report*, descrevemos um caso clínico de um jovem de 19 anos com diagnóstico de uma variante de pequenas células ALK+LAGC com ARDS, ao qual foi

necessário a intervenção por ECMO. Neste caso em particular, o doente melhorou significativamente quando a quimioterapia foi realizada concomitantemente com o suporte por ECMO, devido aos benefícios proporcionados pelo suporte da ventilação mecânica, corroborando os casos clínicos descritos na literatura até ao momento.

Palavras-chave: Linfoma Não-Hodgkin, Linfoma Anaplásico Quinase positivo, Síndrome Respiratória Aguda Grave, Oxigenação por Membrana Extracorporal, Transplante de Medula Óssea.

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ABSTRACT

Anaplastic large T cell lymphoma (ALCL), a group of CD30-positive mature T cell lymphomas, is a rare and aggressive Non-Hodgkin T cell lymphoma (NHL), representing about 1–3% of Non-Hodgkin lymphoma (NHL) and about 15% of peripheral T cell lymphomas throughout the world.

There are four subtypes of anaplastic large cell lymphoma according to the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues: systemic Anaplastic Lymphoma Kinase (ALK) positive (ALK+ALCL); systemic ALK negative (ALK– ALCL); primary cutaneous ALCL (pc-ALCL); and breast-implant associated (BIA-ALCL). These four subtypes are distinguished by their clinical symptoms, genetic characteristics, prognoses and therapy.

The ALCL sinusoidal growth and perivascular distribution pattern, that can be found in approximately 75% of cases, generates a lymphomatous infiltration (pulmonary lymphangitis), resulting in an Acute Respiratory Distress Syndrome (ARDS) that could require mechanical ventilation.

According to the literature, immunocompromised patients show remarkable improvement when treated with the cyclophosphamide, doxorubicin, vincristine and prednisone regimen (CHOP or CHOP plus etoposide (CHOEP), the standard treatment) simultaneously with the use of mechanical ventilation, despite the existence of some contraindications. In such cases, ventilatory support is recommended when there is potential for reversible pulmonary involvement. For Extracorporeal Membrane Oxygenation (ECMO) to be considered as part of the treatment, a robust and efficacious therapeutic approach is required to ensure the potential reversibility of the disease. In this context, ECMO functions as a "bridge" towards the opportunity to administer chemotherapy, which has the potential to reverse the underlying factors contributing to organ failure requiring ECMO support and, consequently, manage the disease.

Herein, we present a clinical case report of a 19-year-old man with ALK+ALCL, with a small cell variant, who developed acute respiratory distress syndrome (ARDS). This patient exhibited remarkable improvement following an ECMO procedure while chemotherapy was also performed, even in the presence of known medical

contraindications. These findings further support the existing literature on similar cases described so far.

Keywords: Non-Hodgkin Lymphoma, Anaplastic Lymphoma Kinase positive, Acute Respiratory Distress Syndrome, Extracorporeal Membrane Oxygenation, Hematopoietic Stem Cell Transplantation.

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LIST OF ABBREVIATIONS

A+CHP	BV, cyclophosphamide, doxorubicin and prednisone
ADC	Antibody-drug Conjugate
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic lymphoma kinase/ receptor tyrosine kinase
ALK+ALCL	Systemic ALK-positive Anaplastic Large Cell Lymphoma
ALK-ALCL	Systemic ALK-negative Anaplastic Large Cell Lymphoma
Allo-HSCT	Allogenic Hematopoietic Stem Cell Transplantation
ARDS	Acute Respiratory Distress Syndrome
ASCT	Autologous Stem Cell Transplantation
BI-ALCL	Breast Implant-associated Anaplastic Large Cell Lymphoma
BRESHAP	Brentuximab Vedotin (BV) Plus ESHAP (Methylprednisolone, Cisplatin, Cytarabine)
BM	Bone marrow
BV	Brentuximab Vedotin (BV)
CD30	Cell membrane protein of the tumor necrosis factor receptor family. Tumor marker
CHP	Cyclophosphamide, Doxorubicin and Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone regimen
CHOEP	CHOP plus etoposide
CHL	Classic Hodgkin's Lymphoma
CHULN	Centro Hospitalar Universitário Lisboa Norte
CR	Complete Remission
CT	Computerized Tomography
DN(A)R status	"Do not attempt resuscitation" order
ECAR	Extracorporeal-assisted Rewarming
ECMO	Extracorporeal Membrane Oxygenation
ELSO	Extracorporeal Life Support Organization
FDA	Food and Drug Administration
FiO ₂	Inspired Oxygen Fraction
GVHD	Graft-versus-host disease
GVT	Graft versus tumor
HDC	High-dose Chemotherapy
HVG	Host versus graft
HL	Hodgkin Lymphoma
HLA	Human leukocyte antigen
HM	Hematological Malignancies
HSCT	Hematopoietic Stem Cell Transplantation
HyperCVAD	Hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone/methotrexate and cytarabine
ICU	Intensive Care Unit
Ig	Immunoglobulin
IHC	Immunohistochemical test
IMC	Intensive Medicine Care
IV	Intravenous

LAGC	Linfoma Anaplásico de Grandes Células T
LNH	Linfoma não Hodgkin
MH	Malignant Histiocytosis
MHC	Major Histocompatibility Complex
NCCN	National Comprehensive Cancer Network (NCCN)
NA	Noradrenaline
NPM	Nucleophosmin
NPM-ALK	Novel chimeric fusion protein between NPM and ALK proteins
NHL	Non-Hodgkin Lymphoma
OMS	Organização Mundial de Saúde
PaO ₂	Partial Pressure of Oxygen in Arterial Blood
pc-ALCL	Primary Cutaneous Anaplastic Large Cell Lymphoma
PDGF	Peptide Regulatory Factor
PDGFR	Platelet-derived Growth Factor Receptor Inhibitor
PD-1	Programmed Cell death Protein 1 inhibitor
PD-L1	Programmed Death-ligand 1 inhibitor
PRESERVE Score	PRedicting dEath for SEvere ARDS on VV-ECMO score
PRESET	PREdiction of Survival on ECMO Therapy
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma not Otherwise Specified
RESP Score	Respiratory Extracorporeal Membrane Oxygenation Survival Prediction
S-ALCL	Anaplastic Large Cell Lymphoma Small Cell Variant
SARS-CoV-2	Coronavirus SARS-CoV-2
SAPS II Score	Simplified Acute Physiology Score
SOFA Score	Sequential Organ Failure Assessment Score
TAP	Thoracic-abdominal-pelvic
TKI	Tyrosine Kinase Inhibitors
VA-ECMO	Veno-arterial Extracorporeal Membrane Oxygenation
VV-ECMO	Veno-venous Extracorporeal Membrane Oxygenation
WHO	World Health Organization
X-ray	X-radiation

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METHOD

The purpose of this work is to present a clinical case and, simultaneously, provide a literature review on the respective topic related to the development of respiratory failure due to Anaplastic Large Cell Lymphoma (ALCL). To achieve this, a bibliographic search was conducted on the *PubMed* and *Google Scholar* search engines using the following keywords: *Hodgkin T cell lymphoma (HL)/ Non-Hodgkin T cell lymphoma (NHL)/ anaplastic large cell lymphoma (ALCL) and its clinical presentation/ Cyclophosphamide, doxorubicin, vincristine and prednisone regimen (CHOP) and CHOP plus etoposide (CHOEP) treatment in ALCL/ Hematopoietic stem cell transplantation (HSCT) and Autologous stem cell transplantation (ALCL)/ Immunotherapy and targeted therapy in ALCL/ Acute Respiratory Distress Syndrome (ARDS) in ALCL/ Extra Corporeal Membrane Oxygenation (ECMO) and chemotherapy in immunocompromised patients/ ECMO and pulmonary lymphoma.*

Articles published since 1972 were included, written in English, with the aim of encompassing the various established scientific knowledge up to the present moment, as well as more recent studies with novelty and impact on clinical practice.

The research accounted for a total of 138 articles in indexed journals. For the purpose of reviewing clinical trials currently under study, the platform <https://clinicaltrials.gov/> was also consulted. FDA and ELSO notification platforms were also consulted to review and obtain information about approved drugs and ECMO guidelines.

In this context, this work aims to describe a clinical case, establishing a connection with therapeutic approaches and scientific studies described up to the present moment.



Chapter I

Introduction

1.1 Anaplastic Large Cell Lymphoma (ALCL)

Anaplastic large cell lymphoma (ALCL), an aggressive Non-Hodgkin lymphoma (NHL), is mostly present in children and young adults (Malcolm *et al.*, 2016). The natural progression of this disease is largely unknown (Malcolm *et al.*, 2016). ALCL is rare among Non-Hodgkin lymphomas comprising an overall of 1-3% (Shustov and Soma, 2019). It comprises 10-30% of pediatric and 5-10% of adult Non-Hodgkin's lymphoma (Amin and Lai, 2007; Vu and Ai, 2018).

ALCL represents a group of malignant T-cell lymphoproliferations sharing morphological and immunophenotypic features, namely a strong and aggressive CD30 expression with a loss of T-cell markers, but differing in clinical symptoms, genetic characteristics, prognosis and therapy (Zhang *et al.*, 2022).

Stein *et al.* (1985) described ALCL for the first time as “anaplastic large cell Ki-1-positive lymphomas” which share identical immunohistochemical characteristics with classic Hodgkin's lymphoma (CHL), but exhibit morphology suggestive of “malignant histiocytosis” (MH) (Stein *et al.*, 1985). A proliferation and cohesive growth pattern of large lymphoid cells, with a tendency to invade lymph node sinuses, simultaneously with a presence of a strong expression of a ki-1 antigen (later designated CD30) define this entity (Stein *et al.*, 1985).

Moreover, although ALCL has been considered as a neoplasm of CHL and MH, further studies confirmed its derivation from T cells (more concretely from a mature post-thymic T-cell), leading to the recognition of ALCL as a unique subtype of peripheral T-cell lymphoma (PTCL) lacking expression of T-cell related surface proteins.



Chapter II

Clinical Case Report

Male, 19-years old, caucasian, autonomous in his daily activities and living with his parents. No relevant personal background to the exception of having smoker and toxicophilic (cannabinoids) habits.

Patient was admitted and hospitalized at Hospital de Évora from 5th to 9th February 2022 due to pericarditis, with electrocardiographic abnormalities, and a past occurrence of myopericarditis. Following the hospital stay, the patient was discharged with non-clarified etiology for this clinical presentation.

On 15th February, the patient returned to the Hospital due to fever (with no response to antipyretic medication), night sweats, unquantified involuntary weight loss, productive cough with mucous sputum and pleuritic pain on the right side. During the physical examination, hepatosplenomegaly and adenopathies, namely supraclavicular, axillary and inguinal lymph node enlargements, were observed. Concurrently, an elevation in inflammatory markers along with hypogammaglobulinemia were detected. Additionally, thoracic-abdominal-pelvic (TAP) computed tomography (CT) scan revealed extensive bilateral lung densifications primarily affecting the lower lung regions.

As a result of experiencing severe respiratory failure and requiring high-flow oxygen therapy, the patient was admitted in the Intensive Care Unit (ICU). A progression into a respiratory insufficiency accompanied by a refractory hypoxemia was observed, whereby the intubation and mechanical ventilation were performed on the 19th of February, 2022. The patient underwent crurarization and was placed in the prone position as part of the medical interventions. Additionally, on the 20th of February, a veno-venous extracorporeal membrane oxygenation (VV ECMO) cannulation procedure was performed by a specialized medical team sent from the Centro Hospitalar Universitário de Lisboa Norte (CHULN) in response to the patient's persistent and unresponsive hypoxemia. The patient was transferred to CHULN, a national recognized center specializing in ECMO treatment. Despite conducting multiple microbiological cultures, including hemocultures and bronchial secretion cultures, no microbial agent has been identified until the date of transfer to CHULN.

While the patient was in CHULN's ICU, there was a deterioration of the patient's condition, leading to the development of distributive shock, requiring high doses of vasopressor support. In response, a regimen of broad-spectrum antibiotic and antifungal therapy was initiated.

Based on a strong suspicion of lymphoproliferative disease, a series of Methylprednisolone (1g) doses were administered over a four-day period (from 25th to 28th of February), resulting in an improvement of the shock experienced by the patient.

Following the excision of the left inguinal lymph node, the performance of bone marrow aspirate and the biopsy while the patient was still on ECMO, a diagnosis of T-cell Non-Hodgkin lymphoma, specifically CD30-positive anaplastic large cell lymphoma (ALK+), with a small cell pattern, was established. Medullary infiltration with 8% of anaplastic lymphoma cells was documented and imaging findings indicated possible infiltration in the spleen and lungs (suggesting splenic and pulmonary involvement as well), establishing the stage IV of the disease according to the “Ann Arbor staging classification for the Non-Hodgkin's Lymphomas” (**figure I**).

The first chemotherapy cycle was started with CHOEP regimen on 3rd of March 2022, while the patient was on ECMO. Distributive shock was solved within the initial 24h after starting CHOEP treatment, leading to the discontinuation of the instituted broad-spectrum antibiotic therapy.

The patient remained on ECMO support for 38 days and was successfully decannulated on the 29th of March, without requiring additional oxygen supply. This positive outcome facilitated a swift discharge from the hospital following the completion of the second cycle of chemotherapy.

The remaining three cycles of CHOEP chemotherapy were administered at the outpatient clinic, with the final cycle completed on the 20th of May. Unfortunately, prior to the beginning of the 6th cycle of chemotherapy, there was a noticeable deterioration and further advancement of the disease. The progression manifested itself again with pulmonary involvement and rapidly progressive respiratory failure and shock. As a result, the decision was made to initiate ECMO support once again, enabling the initiation of second-line treatment.

Urgent rescue treatment with BRESHAP protocol (Brentuximab-Vedotin (BV) + ESHAP (Methylprednisolone, Cisplatin, Cytarabine)) was performed. A rapid and significant response was achieved following the completion of the first cycle of treatment, allowing a rapid weaning of organ support requirements and the potential for discharge.

As a consequence of pulmonary complications, which negatively affected respiratory function, the planned bone marrow transplant could not be carried out. Consequently, the patient received BV therapy in association with off-label use of Crizotinib, following the completion of 4 cycles of BRESHAP therapy. It was chosen as maintenance therapy until either halt disease progression or recovery from the pulmonary complications.

Ann Arbor Classification of Non-Hodgkin's Lymphomas	
Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) alone or with localized involvement of an extralymphatic organ or site (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) alone or with localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement
All patients are subclassified A or B to indicate the absence or presence, respectively, of unexplained weight loss of more than 10% body weight, unexplained fever with temperatures more than 38° C, and night sweats.	

Figure I. Ann Arbor staging classification for the Non-Hodgkin's Lymphomas. This classification is based on the number of lymph node sites, disease above or below the diaphragm, involvement of extranodal sites, and the presence or absence of systemic symptoms (adapted from Skarin and Dorfman, 1997).



Chapter III

Discussion

3.1. ALCL: Clinical Presentation of the Disease

In ALCL, there is a slight male predominance (55.5%), most patients present B-type symptoms (fever (85.18%), night sweats and weight loss) and advanced-stage disease (Hapgood and Savage, 2015; Montes-Mojarro *et al.*, 2018; Sun *et al.*, 2021). Particularly, ALK+ALCL typically occurs in younger patients, mostly occurring in patients younger than 30 years of age (70%) (Stein *et al.*, 2000; Savage *et al.*, 2008; Dowd *et al.*, 2014; Barrese *et al.*, 2017). Extranodal involvement, including skin (21%), bone (17%) and soft tissues (17%), lung (11%), bone marrow (11-30%) and liver (8%) is observed in 60% of the cases and approximately 40% of the patients present two or more extranodal sites of lymphoma (Stein *et al.*, 2000).

According to the World Health Organization (WHO) in 2016, ALCL can be classified in four subtypes, considering their clinical and molecular findings: systemic ALK-positive ALCL (ALK+ALCL), systemic ALK-negative ALCL (ALK-ALCL), primary cutaneous ALCL (pc-ALCL), and breast implant-associated ALCL (BI-ALCL); this last resulting after prolonged exposure to breast implants (Swerdlow *et al.*, 2016).

ALK+ALCL typically occurs in younger patients while ALK-ALCL is more commonly seen in older adults (Savage *et al.*, 2008). Young age has been reported as a strong feature of a favorable prognosis of ALK+ALCL, with 5-year survival rates of 70% to 90%, while ALK-ALCL in older adults represents survival rates of 40% to 60% even in advanced stage, with exception of Small cell variant of ALCL (S-ALCL) (Falini *et al.*, 1999; Stein *et al.*, 2000; Savage *et al.*, 2008; Sibon *et al.*, 2012).

The recognition of these subgroups of ALCL refers to the chromosomal translocations or inversions observed in each entity. Therefore, the recognition of the pathological spectrum of ALCL regarding anaplastic lymphoma kinase (ALK) fusion proteins, as a result from chromosomal modifications, is crucial for the distinction of different subgroups of ALCL and for understanding its pathogenesis (Montes-Mojarro, I.A. *et al.*, 2018).

S-ALCL represents 5-10% of the cases and usually leads to a higher incidence of leukemic involvement in younger patients with unfavorable prognosis (Jagasia *et al.*, 2004; Youd *et al.*, 2009; Grigoropoulos *et al.*, 2013). Interestingly, the survival outcomes

for small cell variant are comparable to those for ALK-ALCL rather than ALK+ALCL (Dowd *et al.*, 2014).

3.2. Small cell variant of ALCL (S-ALCL)

ALCL cells exhibit variably shaped nuclei, namely invaginated, horseshoe/kidney shaped, donut-like or Reed-Sternberg-like nuclei with abundant cytoplasm. Strong immunoreactivity for CD30 is generally observed as well (Tsuyama *et al.*, 2017). Several morphological patterns are visible on ALCL, since various appearances can be detected on this disease: a) exhibition of a large and pleomorphic, b) small-cell, c) Hodgkin-like, or d) sarcomatoid appearance. In all morphological subgroups, tumor cells are large and, therefore, called “hallmark cells” (Benharroch *et al.* 1998). It is important to note that the S-ALCL variant is a histological variant and not an individualized entity in the WHO classification of lymphomas.

While ALK+ALCL is characterized by large and pleomorphic lymphoid cells with abundant cytoplasm and horseshoe-shaped nuclei positive for CD30, in S-ALCL hallmark cells are present in a few number and small to medium-sized tumor cells (Kinney *et al.*, 1993). Kinney *et al.* (1993) reported this pattern as primary Ki-1-positive T-cell lymphoma with histological features different from typical ALCL but still with a t(2;5)(p23;q35) translocation (Kinney *et al.*, 1993). Histologically, in S-ALCL, hallmark cells can usually be identified in and around small vessels and strong CD30 expression may or may not be present in small neoplastic cells. A positive ALK immunostaining with a nucleus-restricted pattern is always exhibited (Falini *et al.*, 1998). *I.e.*, in small cell variant, hallmark cells are few, small, identified around vessels and ALK staining is usually confined to the nucleus. On the other hand, other ALK variants present large hallmark cells, lack nuclear localization and the staining pattern is limited to the cytoplasm (Montes-Mojarro *et al.*, 2018).

Leukemic presentation in ALCL is highly unusual but most often reported in the small cell variant cases (Nguyen *et al.*, 2009; Summers and Moncur *et al.*, 2010; Grigoropoulos *et al.*, 2013). When ALK+ALCL is in its leukemic phase, the prognosis is guarded (Nguyen *et al.*, 2009). Several cases have been identified as leukemic ALCL with a high white blood cell count (average $< 100 \times 10^9/L$) (Nguyen *et al.*, 2009; Gadage *et al.*, 2011; Grigoropoulos *et al.*, 2013; He and Viswanatha, 2013; Imamura *et al.*, 2013).

The high incidence of leukemic peripheral blood involvement is one of the possible explanations for the unfavorable prognosis of this variant (Onciu *et al.*, 2003; Spiegel *et al.*, 2014).

Lung involvement of ALCL occurs in pediatric and adult patients. The sinusoidal growth and perivascular distribution pattern observed in ALCL generates a pulmonary lymphomatous infiltration, which can lead to a severe respiratory distress (Sato and Tamai, 2020). Several studies have reported that alveoli infiltration by tumor cells may result in interlobular septal thickening and granulomatous consolidation which can mimic the appearance of pneumonia, miliary tuberculosis or pulmonary lymphangitic carcinomatosis (Sato and Tamai, 2020). Also, the clusters of large cells congesting the sinuses may mimic a metastatic carcinoma (Benharroch *et al.* 1998).

Han *et al.*, 2014 described a case of primary ALCL in a patient who was initially diagnosed with tuberculosis. ALCL was confirmed only after lymph node biopsy. After a few weeks, the patient developed a total atelectasis of the left lung which could have been fatal if the mass had been considered as a primary lung carcinoma and no empirical steroid treatment to reduce lymphoma-induced acute exacerbation was started (Han *et al.*, 2014).

In our case report, B symptoms were the initial manifestations presented by the patient, highlighting one of the distinctive features of ALCL malignancy. Another initial symptom experienced by the patient was respiratory distress caused by pulmonary involvement, which could initially be associated with pneumonia or tuberculosis.

In this case, no lymphoma cells were detected in the peripheral blood. However, thoracic radiography (**figure II**) and CT scan (**figure IIIa and figure III b1**) revealed pulmonary infiltration with bilateral pulmonary consolidations and pleural effusion, as well as hilar enlargement (**figure III b2**), leading to respiratory failure. Still in CT scan it was possible to observe hepatosplenomegaly (**figure III c1 and c2**), one of the characteristics often reported and observed in these patients. Furthermore, chest, abdomen and pelvis contrast-enhanced CT scans revealed supraclavicular (not represented here), axillary (**figure IV a1**), hilar (**figure IV a2**) and inguinal (**figure IV b1**) lymphadenopathy. The lymph node biopsy indicated the presence of small lymphocytes, and immunohistochemical (IHC) testing (not represented here as well) demonstrated characteristic patterns of ALK+ S-ALCL. Positive ALK immunostaining restricted to the

cell nucleus, strong CD30 expression and small vessels surrounded by hallmark cells were visible on immunohistochemistry, which confirmed the diagnosis of T-cell Non-Hodgkin lymphoma, CD30-positive, anaplastic large cell ALK+, with a small cell pattern.

Small cell variant of ALCL (S-ALCL) can be easily misdiagnosed as primary cutaneous CD30-positive lymphoproliferative disorders (primary cutaneous ALCL, lymphomatoid papulosis), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) and angioimmunoblastic T-cell lymphoma (Stein *et al.*, 1985; Delsol *et al.*, 2008).

Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) (a diagnosis of exclusion, comprising several disease entities that differ in biology, clinical presentation and outcome) can also be considered for differential diagnosis since PTCL-NOS can manifest the same morphology with a variable CD30-positivity (Kinney *et al.*, 1993; Jaffe *et al.*, 2001; Oluwasanjo *et al.*, 2018). Some features are shared for both these subgroups. PTCL-NOS typically occurs in adults (but with a median age of 55-60 years), being more prevalent in males as well. Patients often have B symptoms, generalized lymphadenopathy, bone marrow infiltration, and extranodal involvement, as well as can be seen in S-ALCL (Savage *et al.*, 2011). However, cell morphology and the absence of ALK and antigen expression on epithelial membrane allows to make a distinction from ALCL.

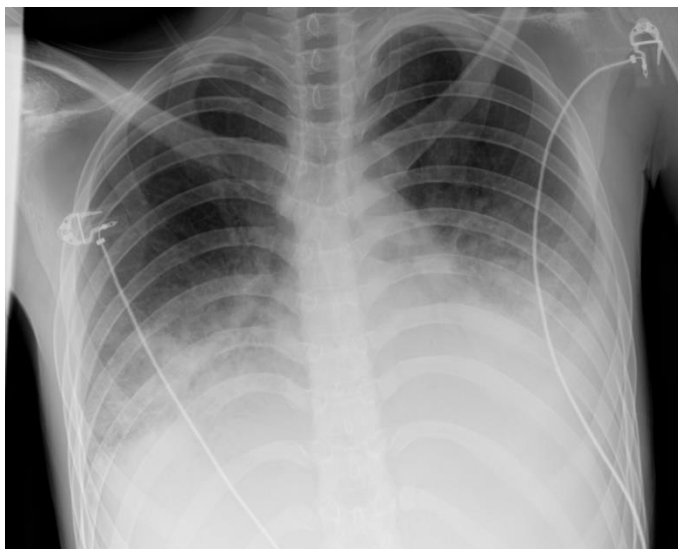
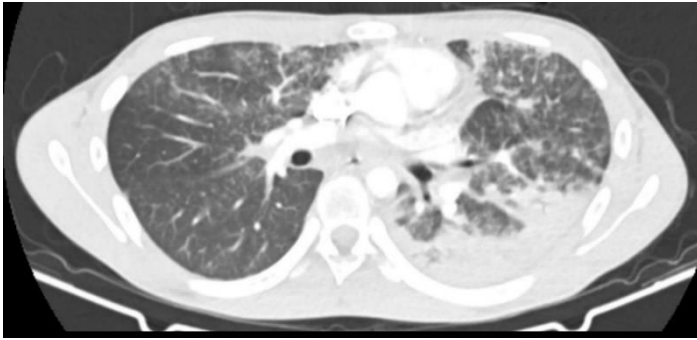
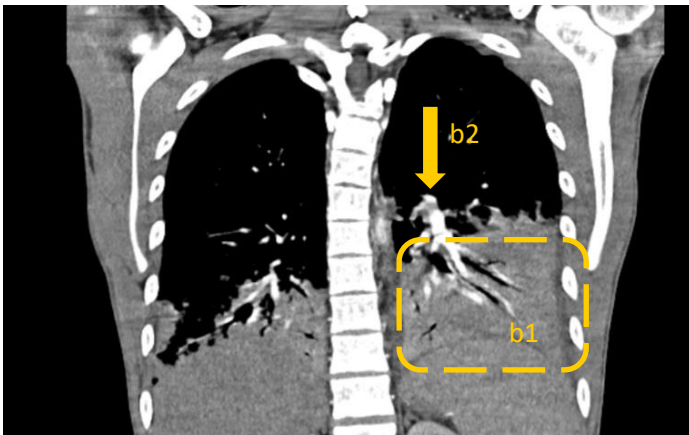


Figure II. X-ray image. Pulmonary involvement: lung infiltrate with bilateral pulmonary densifications. Pleural effusion conditioning respiratory failure.

a)



b)



c)

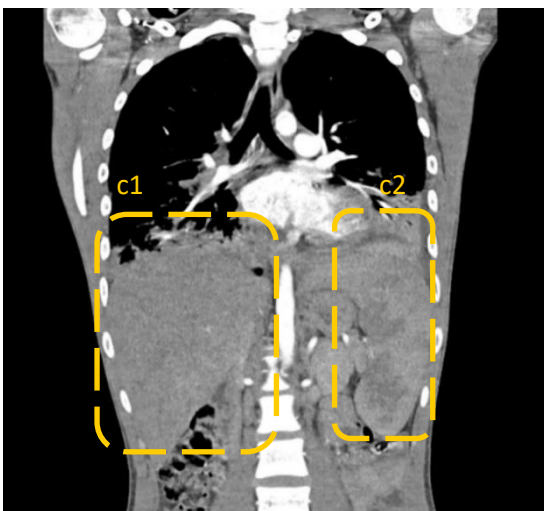
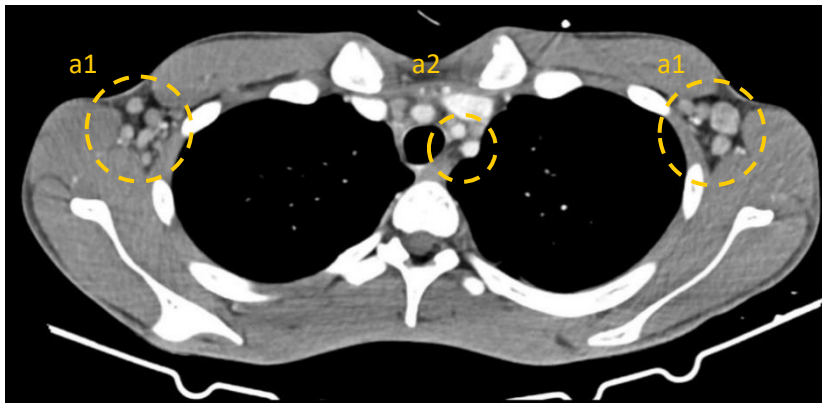


Figure III. Chest and abdominal CT scan: a) Transversal plan: Left pleural effusion and bilateral pulmonary infiltrate, more specifically on the left side; **b)** Coronal plan revealing pleural effusion (**b1**) and hilar enlargement (**b2**), both on the left side; **c)** Coronal plan demonstrating hepatosplenomegaly (**c1** and **c2**).

a)



b)



Figure IV. Chest, abdominal and pelvis transversal CT scan: a) axillary, hilar and **b)** inguinal lymphadenopathy observed on CT. Presence of axillary lymphadenopathy (**a1**) on right and left side. Hilar adenopathy is also observed (**a2**). Inguinal adenopathy more evidenced on patient's left side (**b1**).

3.3. Genetic and Molecular findings in ALK+ALCL

ALK+ALCL represents 60-85% of all ALCL cases and all express ALK fusion genes (Sun *et al.*, 2021). In more than 80% of the cases, ALK+ALCL is characterized by t(2;5)(p23;q25) chromosomal translocation between ALK gene, a receptor tyrosine kinase domain on chromosome 2p23, and the Nucleophosmin (NPM) protein gene on chromosome 5q35, forming the novel chimeric fusion protein NPM-ALK (Morries *et al.*, 1994) (**figure V**). This translocation induces an overexpression and constitutive

activation of a chimeric ALK fusion protein with an important role on oncogenesis processes (Morries *et al.*, 1994; Pulford *et al.*, 2004).

Similar to other fusion oncogenes, activated NPM-ALK interact with downstream signaling molecules, promoting the survival signaling cascade and cell proliferation (Chiarle *et al.*, 2008; Subbiah *et al.*, 2021). Also, ALK represents the insulin receptor superfamily, playing an important role in the pathogenesis of several cancers by either chromosomal translocations or point mutations (Holla *et al.*, 2017).

Nucleophosmin is a nucleolar phosphoprotein responsible for the shuttling of several proteins and nucleic acids between nucleus and cytoplasm (Falini *et al.*, 2020). This translocation consists of the NPM1 amino-terminal oligomerization and the entire ALK carboxy-terminal domains, including the tyrosine kinase domain (Kunchala *et al.*, 2018). Subsequently, the extracellular domain of ALK is lost (Konnath George *et al.*, 2014). The fusion protein NPM-ALK is localized in the cytoplasm but it is also capable of translocating to the nucleus as a result of heterodimerization with wild-type NPM (Bischof *et al.*, 1997).

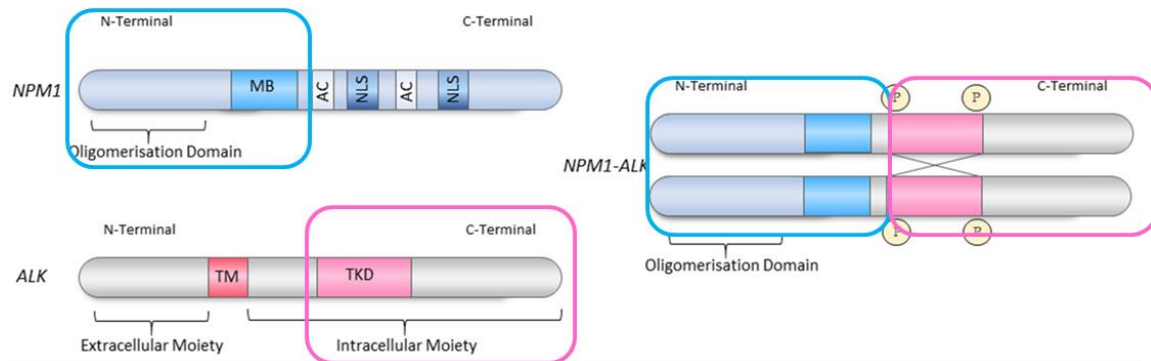


Figure V. Chimeric fusion protein NPM-ALK: t(2;5)(p23;q25) chromosomal translocation in ALK+ALCL, leading to a constitutive activation of ALK-tyrosine kinase and, consequently, to the survival signaling cascade and cell proliferation (adapted from Ducray *et al.*, 2019).

Other ALK chromosomal rearrangements can also occur, namely involving tropomyosin 3-ALK (TPM3: 1q25; 13% of cases (Lamant *et al.*, 1999)), 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC: 2q35; 1% (Ma *et al.*, 2000)), TRK-fused gene-ALK (TFG:3q12.2; 1%, (Hernández *et al.*, 1999)),

moesin-ALK (MSN: Xq11-12; < than 1% (Tort *et al.*, 2001)) as well as other translocations occurred in less than 1% of the cases. **Table I** shows the possible variants ALK fusions.

All the variant translocations lead to the constitutive activation of ALK-tyrosine kinase and represent the crucial modification in this lymphoma (Pulford *et al.*, 2004).

Table I. Genetic and molecular rearrangements in ALCL (adapted from Montes-Mojarro *et al.*, 2018).

DISEASE	CHROMOSOMAL REARRANGEMENTS
ALK+ALCL	Most common rearrangement (80%): NPM1-ALK, t(2;5)(p23;q35)
	Other variant translocations: TPM3-ALK, t(1;2)(p23;q25) AT1C-ALK, inv(2)(p23;q35) TFG-ALK, t(2;3)(p23;q12) CTLC-ALK, t(2;17)(p23;q23) MSN-ALK, t(2;X)(p23;q11-12) TPM4-ALK, t(2;19)(p23;p13) MYH9-ALK, t(2;22)(p23;q11) RNF213-ALK, t(2;17)(p23;q25) TRAF-1-ALK, t(2;9)(p23;q33)
	IRF4-DUSP-22, 6p25.3 (30%)
	TP63-TBL1RXR1, 3q28 (8%)
	JAK-1 and STAT3 mutations variants resulting in STAT3 or JAK-1 constitutive activation:
	NKB2, ROS1
	NCOR2-ROS1
	NFKB2-TYK2
	PABPC4-TYK2

3.4. Targeted/Immunotherapy

The overall survival and relapse or refractory outcomes have barely improved in the ALCL (Larose *et al.*, 2019; Sun *et al.*, 2021). Therefore, an increased number of novel target therapies are being studied and tested in previous years and recent advances in this field are being implemented in clinical practice (Sun *et al.*, 2021).

ALK inhibitors, BV and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors are some examples of new therapies recently tested for ALCL.

BV is an antibody-drug conjugate (ADC) approved by Food and Drug Administration (FDA) in August 2011 for patients who failed the first-line multiagent chemotherapy (U.S. Food and Drug Administration. 2011 Notifications). This antibody is capable of targeting CD30 antigen (a member of the tumor necrosis factor receptor superfamily) present on the surface of malignant cells, inducing a high cytotoxicity and consequently a high anti-tumor activity with low side effects, simultaneously (Shustov *et al.*, 2019).

Crizotinib, an ALK inhibitor, showed promising clinical responses in ALCL and non-small cell lung cancer (Kwak, *et al.*, 2010; Gambacorti-Passerini *et al.*, 2011). Crizotinib was the first ALK inhibitor used as a standard of care for ALK cancers but, unfortunately, not every patient responds and invariably relapse to this drug. Clinical data has demonstrated resistance to this drug due to acquired mutations or amplifications on ALK gene (Katayama *et al.*, 2012; Doebele *et al.*, 2012). Ceritinib was developed and approved by FDA to overcome the crizotinib-resistant disease (Chen *et al.*, 2013). This ALK inhibitor demonstrated to be able to bind to ALK gene with higher affinity compared with crizotinib since it overcome two of the most common ALK-mutants that confer resistance to crizotinib (Friboulet *et al.*, 2014; Santarpia *et al.*, 2017).

Although BV and ALK inhibitors, alongside with other recently studied therapies, have demonstrated promising outcomes and favorable survival rates for patients with ALK+ALCL, their utilization as first-line treatments require additional investigation. Specifically, phase III clinical trials encompassing a representative sample should be conducted to attempt achieving considerable and substantial evidence of their safety and efficacy, which is particularly challenging to obtain in the case of rare conditions such as ALCL.

mTOR inhibitors are an important downstream protein kinase which contributes for tumorigenesis. This kinase can be detected in about 80% of patients with ALCL, being associated to ALK expression (Liu and Sabatini, 2020). Thus, mTOR inhibitors can decrease the phosphorylation of mTOR inducing apoptosis of tumor cells (Jundt *et al.*, 2005). mTOR inhibitors such as Everolimus have been studied in clinical trials, alone or in combination with CHOP, demonstrating good results so far (Johnston *et al.*, 2016;

Johnston *et al.*, 2018; Witzig *et al.*, 2018). Rapamycin, another mTOR inhibitor, also demonstrated to be efficient in leukemia and other hematological malignancies (HM) when other treatments applied are not well-succeeded or when a treatment resistance response is observed, revealed a complete remission (Chumsri *et al.*, 2008; Teachey *et al.*, 2009).

Moreover, some studies have demonstrated that the combination of ALK inhibitors and mTOR inhibitors can improve the effectiveness of treatments in ALK+ALCL patients (Xu *et al.*, 2018; Kim *et al.*, 2020).

Furthermore, PD-1/PD-L1 inhibitors have also been studied. PD-1 is a receptor protein of the PD-L1 ligand. This receptor is expressed on activated T cells and PD-L1 is expressed in a variety of tumor cells. The interaction of these two proteins induces a negative regulatory signal to T Cells, leading to an immune escape of tumor cells by inhibiting their activation, proliferation and cytokine production (Freeman *et al.*, 2000; Lu *et al.*, 2019). Therefore, control PD-L1 ligand expression in ALK+ALCL can induce durable tumor remissions in patients with diverse advanced cancers and decrease the immune escape of the tumor (Sun *et al.*, 2018; Zhang *et al.*, 2020). Nivolumab, pembrolizumab and atezolizumab (monoclonal antibodies targeting PD-1 or PD-L1) have been studied in clinical trials. Nivolumab and pembrolizumab were approved in 2015 and 2018, respectively, by FDA (Lu *et al.*, 2019).

Platelet-derived growth factor receptor (PDGFR) inhibitors are another class of therapy that have been widely studied (Heldin *et al.*, 2018). PDGF is a peptide regulatory factor that binds to PDGFR (its receptor), activating the PDGF-PDGFR pathway, inducing cell proliferation and survival of lymphoma cells (Sun *et al.*, 2021). Interestingly, Laimer *et al.* (2012) showed that NPM-ALK transgenic mice significantly exhibit a higher and prolonged survival time after the inhibition of PDGFR. Still in this study, they also reported a case of a 27-years-old patient with a stage III ALK+ALCL who achieved a rapid complete remission maintained for 22 months, with a decrease levels of tumor marker after a treatment with imatinib, a PDGFR inhibitor-like, for 10 days with no recurrence one year after the drug withdrawal (Laimer *et al.*, 2012; Laimer-Gruber, 2014). It is important to refer that this patient was unresponsive to conventional chemotherapy and relapsed following autologous stem cell transplantation (ASCT) (Laimer *et al.*, 2012).

The expensive costs and the challenges inherent to the immunotherapy effectiveness, prediction of the efficacy for each patient and to the side effects or drug resistance have been some of the reasons for immunotherapy limitations (Sun *et al.*, 2021).

Nevertheless, several clinical trials are ongoing for ALCL/ALK+ALCL as can be seen in **Table II**.

Several targeted therapies have been widely studied and the emergence of new drugs and immunotherapies have been developed to provide new opportunities for patients with ALCL. It is hoped that new molecular mechanisms could be clearly studied in the future to improve overall survival and the progression-free survival of these patients.

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Table II. Ongoing Clinical Trials of ALCL and ALK+ALCL (<https://clinicaltrials.gov>)

Clinical Trial ID	Status	Conditions	Interventions	Phase	Patient Number Enrolled
NCT04925609	Recruiting	-Anaplastic Large Cell Lymphoma, ALK-Positive; -Inflammatory Myofibroblastic Tumor; - Other Solid Tumor	Drug: Brigatinib	Phase 1 Phase 2	65
NCT04423926	Recruiting	- PTCL, NOS; - Angioimmunoblastic T-cell lymphoma (AITL); - ALK-ALCL (and 2 more...)	Drug: Lenalidomide Drug: Cyclophosphamide Drug: Doxorubicin (and 2 more...)	Phase 1 Phase 2	91
NCT03703050	Recruiting	Relapsing/Refractory ALK+ Anaplastic Large Cell Lymphoma	Drug: Nivolumab cohort 1 Drug: Nivolumab cohort 2	Phase 2	38
NCT02419287	Active, not recruiting	Anaplastic Large Cell Lymphoma, ALK-Positive	Drug: crizotinib	Phase 2	12
NCT03505554	Recruiting	Anaplastic Large Cell Lymphoma, ALK-Positive	Drug: Lorlatinib	Phase 2	12
NCT03603847	Recruiting	Anaplastic Large Cell Lymphoma, ALK-Positive		Observational	40

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NCT03971305	Recruiting	- Lymphoma Non-Hodgkin - Minimal residual disease (MRD) - Minimal disseminated disease (MDD)		Observational	300
NCT04439266	Active, not recruiting	- Advanced Lymphoma; - Advanced Malignant Solid Neoplasm; - Hematopoietic and Lymphoid Cell Neoplasm (and 3 more...)	Drug: Crizotinib	Phase 2	5
NCT04908059	Recruiting	Anaplastic Lymphoma			2
NCT01979536	Active, not recruiting	- Anaplastic Large Cell Lymphoma, ALK-Positive; - Ann Arbor Stage II Noncutaneous Childhood Anaplastic Large Cell Lymphoma; - Ann Arbor Stage III Noncutaneous Childhood Anaplastic Large Cell Lymphoma; - Ann Arbor Stage IV Noncutaneous Childhood Anaplastic Large Cell Lymphoma	Drug: Brentuximab Vedotin Drug: Crizotinib Drug: Cyclophosphamide (and 6 more...)	Phase 2	137
NCT02223208	Active, not recruiting	- Peripheral T-cell Lymphomas (PTCL); - PTCL-NOS; - Angioimmunoblastic T-cell Lymphoma (AITL) (and 2 more...)	Drug: Ro-CHOEP-21 (PHASE I) Drug: Ro-CHOEP-21 (PHASE II)	Phase 1 Phase 2	89
NCT01524926	Active, not recruiting	- Locally Advanced and/or Metastatic Anaplastic Large Cell Lymphoma	Drug: Crizotinib (PF-02341066)	Phase 2	582

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		- Locally Advanced and/or Metastatic Inflammatory Myofibroblastic Tumor - Locally Advanced and/or Metastatic Papillary Renal Cell Carcinoma Type 1 (and 3 more...)			
NCT05160922	Recruiting	- Non-small cell lung cancer (NSCLC) - Anaplastic Large Cell Lymphoma - Inflammatory myofibroblastic tumor (IMT)	Drug: crizotinib	Phase 4	80

3.5. Current Treatment Approach

Currently, anthracycline-based cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) regimen is the first-line therapy for ALCL, demonstrating a significantly superior prognosis of patients with ALK+ALCL in comparison with patients with ALK-ALCL (Sun *et al.*, 2021).

However, more than 50% of patient relapse within 5 years even after a good initial response to CHOP therapy (Limat *et al.*, 2003; Susanibar-Adaniya and Barta, 2021).

In 2010, Schmitz *et al.* suggested a possible benefit from the integration of etoposide in the first-line therapy. In this study, two therapeutic regimens were applied for patients with ALCL (ALK+ALCL and ALK-ALCL): 6-8 courses of CHOP or 6-8 courses of CHOP plus etoposide (CHOEP). For patients ≤ 60 years, three-year event-free survival (EFS) for those who received CHOEP therapy were significantly superior in comparison to those who received the CHOP regimen, even without an improvement of the overall survival (Schmitz *et al.*, 2010).

However, for patients aged > 60 years, no beneficial or obvious effects were observed with the integration of etoposide, whereby 6 courses of CHOP administered every 3 weeks remains the standard therapy for this age group (Schmitz *et al.*, 2010).

In 2019, Sibon *et al.* demonstrated that CHOEP treatment improved not only the progression-free survival but also the overall survival for ALK+ALCL patients. Moreover, this study demonstrated that the incidence of relapse in 5 years noticeably decreased from 37% to 17% after adding the etoposide for these patients (Sibon *et al.*, 2019).

Several alternative therapies have also been studied, such as hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone/methotrexate and cytarabine (hyperCVAD) (Escalon *et al.*, 2005; Abramson *et al.*, 2014); hyper-CHOP (Escalon *et al.*, 2005); and etoposide, ifosfamide and cisplatin-reinforced doxorubicin, bleomycin, vinblastine and dacarbazine (Simon *et al.*, 2010). None of them exhibited better results, to the exception for hyperCVAD, which is still controversial regarding its improvement for progression-free survival rate (Escalon *et al.*, 2005; Abramson *et al.*, 2014). Also, besides intensive regimens represent a higher response rate in comparison with traditional chemotherapy, such as CHOP regimen, a higher toxicity induced remains a challenge (Sun *et al.*, 2021).

So far, CHOP/CHOEP treatment is considered the first-line therapy option for patients with ALCL, with acceptable safety profile and the final outcomes related to survival rate. Young patients benefit more after CHOEP treatment while CHOP regimen remains recommended for elderly patients.

Recently, Horwitz *et al.* (2018) published a phase 3 study, denominated ECHELON-2 study, in which 226 patients with previously untreated CD30-positive peripheral T-cell lymphomas were randomly assigned to received one of two treatments: BV, cyclophosphamide, doxorubicin and prednisone (A+CHP) *versus* cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). The aim of this clinical trial was to evaluate the efficacy and safety of the addition of BV to cyclophosphamide, doxorubicin and prednisone (CHP) and to compare with the first line treatment already applied in clinical practice (CHOP). This trial demonstrated that higher rates of progression-free and overall survival were achieved after the association of BV to CHP with no additional toxicity compared to CHOP treatment.

Hence, considering the notable advancements, manageable safety profile and emerging status as the new standard of care for CD30-positive peripheral T-cell lymphoma patients, BV was considered in this particular case. A favourable response was observed after the first cycle with BRESHAP (when BV was incorporated alongside with ESHAP).

3.6. Treatment of relapsed or refractory disease

ALK TKI resistance is a major challenge in the treatment of ALK+ ALCL (Wang *et al.*, 2022). In this particular case, the patient proved to be refractory to the first line treatment. Upregulation of Bcl-2 gene, ALK amplification, bypass signaling, autophagy and apoptosis are part of the resistance mechanisms that remain to be elucidated and which could explain the resistance in the treatment of ALK+ALCL (Wang *et al.*, 2022).

It has been described a highly effective remission induction when BRESHAP is used prior to transplant in patients with refractory or relapsed Hodgkin lymphoma (Garcia-Sanz *et al.*, 2016; Garcia-Sanz *et al.*, 2019) but no studies have been reported regarding its use in NHL so far.

BRESHAP is usually used in Hodgkin lymphoma and BV is nowadays approved for the treatment of patients with HL and ALCL.

In our case, an urgent rescue therapy with BRESHAP treatment was afterwards implemented due to the patient's lack of response to initial treatment and the presence of pulmonary involvement and distributive shock.

Considering the severity of the situation, which required the patient to be placed back on ECMO and a need for rapid clinical improvement, the decision was made to combine BV with ESHAP. This combination was chosen with the expectation of achieving a more substantial and potentially immediate response. It is worth noting that the use of BRESHAP treatment in NHL was a novel approach for the team, specifically for this patient's unique circumstances.

3.7. Hematopoietic Stem Cell Transplantation (HSCT)

In some cases, due to the unfavorable prognosis and lack of sustained response to chemotherapy of S-ALCL (or other hematological malignancies), HSCT has been investigated as a promising strategy that can be combined with the chemotherapy regimen to improve the overall survival and progression free survival of these patients (Onciu *et al.*, 2003; Summers and Moncur *et al.*, 2010).

Hematopoietic stem cell transplantation is a well-established and effective treatment for various conditions, including malignant hematologic diseases, as well as non-malignant congenital and acquired disorders affecting the hematopoietic system and certain types of solid tumors (Ljungman *et al.*, 2010; Gratwohl *et al.*, 2010). Hodgkin's disease and non-Hodgkin lymphomas can be effectively treated, and in many cases, cured, through initial chemotherapy or radiotherapy. However, like as many other diseases, relapse is common and the necessary treatment involves high doses of chemotherapy (HDC). Thanks to the use of hematopoietic reconstitution using either autologous or allogeneic stem cells after chemotherapy, has made HDC relatively safe, with some centers reporting mortality rates as low as 2% (Rzepecki, 2021).

Some studies have been conducted regarding HDC followed by autologous hematopoietic stem cell transplantation in lymphomas management as a consolidation

therapy for patients with a unfavorable prognosis or with relapsed/refractory disease (Rzepecki, 2021).

Hematopoietic stem cell transplantation is currently performed in two distinct ways: autologous HSCT (ASCT) and allogeneic HSCT (allo-HSCT), each with specific objectives. ASCT is used to restore hematopoiesis after administering high-dose myeloablative chemotherapy, primarily in cases of multiple myeloma and relapsed lymphomas (Majhail *et al.*, 2015). The allo-HSCT allows an adoptive transfer of an immune system from a donor. However, this approach carries the risk of nonspecific immune-mediated toxicity known as graft-versus-host disease (GVHD) (Goldsmith *et al.*, 2020).

Autologous hematopoietic stem cell transplantation is a common treatment option used for various NHLs, particularly as a rescue therapy. In certain subtypes, it is the preferred choice in the first complete remission. The response to chemotherapy before the transplant, whether it is a partial or complete response (chemosensitivity), plays a crucial role in determining the overall outcomes of the procedure (Mir and Bashir, 2019).

HSCT is a regenerative treatment strategy in which the recipient's bone marrow depleted by a cytotoxic conditioning regimen (creating a "space" for the graft in order to minimize a rejection and graft failure) is repopulated and replaced by the donor's hematopoietic stem and progenitor cells (Bettinotti, 2022). In non-malignant diseases, HSCT may function as a curative treatment by replacing the non-functional cells of the bone marrow with the complete functional donor-derived hematopoietic system. On the other hand, for hematologic malignancies and solid tumors, HSCT works as an immunotherapy form in which the immune cells of the donor are able to control the residual malignant cells through the recognition of non-self-targets known as the graft versus tumor (GVT) effect (Bettinotti, 2022).

In 1958, Dausset published the discovery of the human Major Histocompatibility Complex (MHC) of man: the human leukocyte antigen (HLA) system (Dausset, 1958). The MHC/HLA represents a specific group of molecules expressed on the cell surface that assumes a crucial role for the recognition of foreign molecules by the acquired immune system (Bertaina and Andreani, 2018). Thus, the function of HLA molecules is to bind and exhibit antigens derived from pathogens on the cell surface, presenting them to the

T lymphocytes. HLA is a cluster of more than 200 genes located on chromosome 6 (6p21.3) and can be classified in three major groups: HLA class I, HLA class II and HLA class III (Horton *et al.*, 2004).

Later, some studies demonstrated the importance in understanding this mechanism. Thomas *et al.* (1957) induced an intravenous infusion of bone marrow (BM) in patients after radiation and chemotherapy regimen but with devastating effects, high incidence of rejection, graft versus host disease (GVHD) and opportunistic infections.

The success of HSCT is influenced by various factors. Understanding of the fundamental role of the MHC system in host versus graft (HVG) and GVHD reactions led to the firsts clinical breakthroughs in the last years. One major obstacle is the polymorphism of the classical HLA genes. The use of HLA identical siblings as donors has been the key in the successful of BM transplants. Physicians must carefully choose a potential donor with compatible HLA gene to minimize the risk of graft failure GVHD and mortality, while increasing the chances of disease-free survival (Lee *et al.*, 2007; Loiseau *et al.*, 2007). However, due to the vast diversity of HLA alleles and haplotypes, finding an unrelated donor with a precise allelic match as well as conceiving strategies to provide HSCT from HLA-haploidentical family donors safe and feasible remains a challenging effort for the majority of patients over the past decades (Robinson *et al.*, 2013; Russo *et al.*, 2018).

Regarding ALCL particularly, patients with ALK+ALCL and ALK-ALCL show 86% and 68% of complete remission (CR) rates, respectively, after first-line treatments (Sibon *et al.*, 2012). However, more than 40% of patients relapse (Brugières *et al.*, 2000; Savage *et al.* 2008). In this context, several studies have tried to determine the effects of HDC or ASCT treatment in patients with ALCL to decrease relapse after the first remission (D'Amore *et al.*, 2012; He *et al.*, 2012; Mehta *et al.*, 2013; Wilhelm *et al.*, 2016). However, besides all the attempts to understand the advantaged of doing HDC/ASCT, some results are inconsistent or remain unclear, which highlight the necessity of new studies to prove and understand their effectiveness/side effects and all the clinical implications.

Since favorable results are being seen after the traditional chemotherapy used as first-line therapy, ASCT is not recommended as a first complement option for

ALK+ALCL patients (Sun *et al.*, 2021). According to the National Comprehensive Cancer Network (NCCN) guidelines (Horwitz *et al.*, 2020) and to the clinical practice recommendation of the American Society for Blood and Marrow Transplantation (Kharfan-Dabaja *et al.*, 2017), ASCT is recommended mostly for PTCL patients who reach the first complete remission. In this group, considering the recent studies, only ALK-ALCL patients benefit from ASCT. Recently, Park *et al.* (2019) and Fossard *et al.* (2018) demonstrated that overall survival rate could be improved in ALK-ALCL patients after ASCT being used as a first-line consolidation therapy.

Perform ASCT or allo-HSCT is still controversial, sometimes. Two retrospective studies were conducted by European Society for Blood and Marrow Transplantation to realize the efficacy of HSCT. For patients who received ASCT, the incidence of relapse, progression-free survival and overall survival were 34%, 64% and 73%, respectively, and 40%, 53% and 74% for patients who received allo-HSCT.

A retrospective study was conducted by International Blood and Bone Marrow Transplantation Research Center to compare the effectiveness of ASCT and allo-HSCT (Smith *et al.*, 2013) in 112 patients with ALCL (ALK type was indetermined). Outcomes demonstrated that patients who had undergone ASCT present a higher three-year overall survival rate and a lower treatment-related mortality compared to patients who received allo-HSCT after the first complete remission, even without an improvement of progression-free survival or recurrence/progression compared with allo-HSCT (Smith *et al.*, 2013).

More recently, several studies reported CR and good outcomes after allo-HSCT in HL and NHL patients who relapse to initial conventional treatment (Schmitz *et al.*, 2002; Smith *et al.*, 2013, Dowd *et al.*, 2014; Jain *et al.*, 2018), describing HSCT as potential therapy for these patients.

Dowd *et al.*, (2014) reported a case of a 31-year-old female diagnosed with S-ALCL who has achieved an ongoing CR for 116 months after allo-HSCT. Jain *et al.* (2018) also described a rare case of S-ALCL in an 11-year-old girl who was successfully treated with allo-HSCT.

Also, currently, based on the NCCN guidelines, ASCT or allo-HSCT can be performed in patients who experienced a relapse and achieved a partial or complete response following second-line treatment (Sun *et al.*, 2021).

The initial treatment plan for this patient involved a bone marrow transplant. However, due to the worsening of the disease and the presence of pulmonary impairment, the patient was not eligible for the transplant. Consequently, it was decided to implement a maintenance therapy approach by combining BV with Crizotinib, with the goal of managing the disease until the patient's recovery from the pulmonary complications.

3.8. Extracorporeal membrane oxygenation (ECMO)

Acute respiratory failure is the most common diagnosis warranting in intensive care unit (ICU) admission in patients with HM such as leukemia, lymphoma, and multiple myeloma (Wohlfarth *et al.*, 2014). Due to inherent malignancies or due to treatment complications, patients with HM's present a higher risk to develop ARDS (Zhang *et al.*, 2022). The mortality associated to ARDS remains high nowadays (Prasertsan *et al.*, 2019; Yehya *et al.*, 2020) and ECMO can be useful in patients in who mechanical ventilation is unsuccessful (Combes *et al.*, 2020; Cui *et al.*, 2022; Thompson *et al.*, 2022). Acute respiratory distress syndrome (ARDS) is, therefore, the primary indication for the use of ECMO (Yu *et al.*, 2022). In acute leukemia (AL), leukocyte infiltrates, immune activation and pulmonary edema are responsible for 45%-60% of respiratory situations which can lead to ARDS (Chaoui *et al.*, 2004; Azoulay *et al.*, 2015). In ALCL, particularly, the characteristic sinusoidal growth pattern induces a pulmonary lymphangitis, causing a severe respiratory distress (Sato and Tamai, 2020).

Recent advances in chemotherapy and hematopoietic stem cell transplant (HSCT) have improved the clinical course of these patients (Bay *et al.*, 2013; William and Lima, 2013). However, these patients often develop life-threatening complications, namely lung complications such as pneumonia, pulmonary hemorrhage and bronchiolitis obliterans (Poletti *et al.*, 2000; Haddad, 2013). It is also known that up to 40-50% of hospitalized patient eventually require mechanical ventilation, even if they have undergone or benefited from chemotherapy and HSCT (Yeo *et al.*, 2012; Bay *et al.*, 2013).

Extracorporeal membrane oxygenation is a type of advanced life support technology used as an alternative or rescue treatment for patients with ARDS (Combes

et al., 2018). In this procedure, venous blood is drain from the patient, forwarded to an artificial filter to be oxygenated (carbon dioxide is removed and oxygen provided) and returns to the patient, acting as a cardiopulmonary bypass (Makdisi and Wang, 2015; Quintel *et al.*, 2020).

Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure was first reported on 1971 and represent the beginning of ECMO support as we know it today (Hill *et al.*, 1972; Featherstone and Ball, 2018).

ECMO is recommended in international guidelines not only for patients with severe acute respiratory failure but also to whom with cardiogenic shock with a high risk of mortality (80%) when conservative measures, such as inotropic support and/or placement of an intra-aortic balloon pump, are unsuccessful (Brogan *et al.*, 2017; Fichtner *et al.*, 2018; Ratnani *et al.*, 2018; Fichtner *et al.*, 2019).

In the last decades, ECMO support has been widely used, namely for the treatment of lung or heart transplant, resuscitation of patients with severe traumas or extracorporeal-assisted rewarming (ECAR) of accidental hypothermia (Rajic *et al.*, 2022).

Indications and contraindications should be determined and must be considered to anticipate if an individual patient will benefit from this treatment, a decision that often decides life or death for the patient. Harnisch and Moerer (2021) developed an easy-to-follow algorithm that incorporates absolute and relative contraindications to ECMO treatment, based on literature. According to this study, absolute contraindications were identified, namely: a) refusal of the use of ECMO by the patient, b) advanced stage of cancer, b) fatal intracerebral hemorrhage, cerebral herniation or intractable intracranial hypertension, c) irreversible destruction of the lung parenchyma without the possibility of transplantation and d) contraindications to lung transplantation. Relative contraindications comprise a) advanced age, b) immunosuppressed patients/pharmacological immunosuppression, c) injurious ventilator settings > 7 days, d) right-heart failure, e) HM, especially bone marrow transplantation and graft-versus-host disease, f) SAPS II score ≥ 60 points, g) SOFA score > 12 points, h) PRESERVE score ≥ 5 points, i) RESP score ≤ -2 points, j) PRESET score ≥ 6 points, and k) “do not attempt resuscitation” order (DN(A)R status). Here, as well as in other studies, immunosuppressed patients/pharmacological immunosuppression and

HM are described as relative contraindications for the initiation of ECMO and not as absolute contraindications for its use.

The most frequent complications of ECMO are hemorrhagic and thrombotic events, acute renal and multiorgan failure as well as infection (Aubron *et al.*, 2013; Schmidt *et al.*, 2015; Abrams and Brodie, 2017; Kim *et al.*, 2021). Among complications acquired during ECMO, sepsis stands out prominently. Some studies demonstrated that more than 40% of patients developed sepsis after they underwent to ECMO (Allyn *et al.*, 2018; Peitz *et al.*, 2018).

Immunosuppression condition, high severity of underlying illness and a large used number of indwelling medical devices and procedures represent the main risk factors for sepsis events (Gopalakrishnan and Vashisht, 2021). The higher the age (Aubron *et al.*, 2013), time duration of ECMO (Kim *et al.*, 2017) and number of foreign devices (O'Neill *et al.*, 2001) and comorbidities (Sun *et al.*, 2010), the higher is the risk factors for developing septic complications in ECMO. The risk of complications using ECMO is increased by the complex clinical conditions of patients with HM (Azoulay *et al.*, 2013; Lee *et al.*, 2017). Moreover, cytopenia and extended periods of marrow aplasia are often observed when additional chemotherapy is used, which leads to a higher susceptibility to bacteria, virus and fungus infections (Azoulay *et al.*, 2013; Lee *et al.*, 2017). Thus, all those factors are considered and have been associated with a high-risk state in patients with hematological malignancies on ECMO (Azoulay *et al.*, 2013; Lee *et al.*, 2017).

Previous studies reported poor outcomes in these patients under ECMO, in some cases with mortality rates from 64% up to 85% (Yeo *et al.*, 2012; Azoulay *et al.*, 2014; Rabe *et al.*, 2015; Schmidt *et al.*, 2018). Kang and colleagues (2015) published a retrospective review reporting that patients with HM who required ECMO had poor outcomes. The incidence of complications in these patients did not significantly differ from that in immunocompetent patients and it was even associated with an increased mortality due to the development of infections (Kang *et al.*, 2015). Schmidt *et al.* (2018) reported a low 6-month survival of the large cohort of immunocompromised patients studied, supporting the idea of restricting ECMO only for patients with acceptable functional status and few pre-ECMO mortality-risk factors (Schmidt *et al.*, 2018; Kochanek *et al.*, (2022)

Due to these all reasons, ECMO is rarely used for patients with malignancies in clinical practice, since it is frequently associated with complications and injuries (Yu *et al.*, 2022).

However, the use of ECMO in patients with HM who develop ARDS have been controversial (Combes *et al.*, 2018; Huprikar *et al.*, 2019; Kochanek *et al.*, 2022). In some particular circumstances, ECMO may be used for severe circulatory and/or respiratory dysfunction as was already reported (Cho *et al.*, 2019) or can also be used to stabilize patient with malignancy through chemotherapy (Prabhu *et al.*, 2012).

As it is described later herein, recently studies have demonstrated the opposite and that some patients with aggressive malignancies can really benefit from ECMO (Aboud *et al.*, 2008; Oto *et al.*, 2014; Wohlfarth *et al.*, 2014; Allain *et al.*, 2015; Worku *et al.*, 2015; Huprikar *et al.*, 2019; Sato and Tamai, 2020).

Aboud *et al.*, (2008) reported a successful case of a 43-year-old woman with Non-Hodgkin lymphoma with acute respiratory insufficiency due to a bulky mediastinal mass, which compromises the trachea, after ECMO treatment. Patient was treated with chemotherapy regimen (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone, and Rituximab) while on extracorporeal life support. Discharge was accomplished after a 36-day in the ICU, with normal pulmonary function and a complete remission (Aboud *et al.*, 2008).

Huprikar and colleagues (2019) conducted a retrospective review of patients with acute myeloid leukemia and ARDS requiring ECMO support. 75% decannulation rate and 50% 1-year survival was achieved while undergoing induction chemotherapy (Huprikar *et al.*, 2019).

Sato and Tamai (2020), described a 29-year-old man case report with hypoxemia and generalized lymphadenopathy and splenomegaly, simultaneously, who underwent to mechanical ventilation. Afterwards, ALK+ALCL were confirmed by inguinal lymph node biopsy and chemotherapy accomplished with CHOP treatment while ECMO was induced. ECMO and CHOP treatment remarkably improved the ventilatory parameters and patient was extubated 3 days after chemotherapy being initiated (Sato and Tamai, 2020). However, due to the underlying risk in patients with malignancy, the eligibility of patients with cancer for ECMO ventilation is still an ongoing controversy.

Also, according to the Extracorporeal Life Support Organization (ELSO- a nonprofit organization who maintains the worldwide registry of ECMO support in active ELSO centers) guidelines no absolute contraindications are described to administering chemotherapy when on ECMO for patients with HM (ELSO guidelines, 2022). Still according to ELSO guidelines, a hospital discharge rate of 58% in adults and 69% in pediatric pulmonary after ECMO support was achieved (ELSO guidelines, 2022).

ECMO has also been reported as a bridge through the chemotherapy in patients with lymphoma who develop shock. Worku *et al.*, (2015) described a 41-year-old woman case who present cardiogenic shock after starting chemotherapy (Dexamethasone, Etoposide, Adriamycin, and Vincristine), requiring emergent intubation. ECMO was initiated as a bridge to treatment, receiving, simultaneously, one cycle of chemotherapy for 5 days, while in ECMO. Complete cardiopulmonary functions were recovered (Worku *et al.*, 2015).

More studies have also been revealed good outcomes for patients with HM requiring ECMO support, even in situations of shock, with long-term survival, complete remission and/or with favorable prognosis after HSCT (Oto *et al.*, 2014; Wohlfarth *et al.*, 2014; Allain *et al.*, 2015; Worku *et al.*, 2015).

In Portugal, the use of ECMO outside the context of cardiac surgery was first implemented at CHULN in May 2010 during the Influenza A H1N1 pandemic, as documented by Meireles *et al.* (2021). Subsequently, in 2017, CHULN was officially recognized as a national referral center for ECMO, encompassing three distinct divisions: respiratory adult venovenous ECMO (VV-ECMO), cardiac adult venoarterial ECMO (VA-ECMO) and the neonatal and pediatric ECMO (both VV and VA) (Meireles *et al.*, 2021).

In the case of our patient, a single cycle of CHOEP and BRESHAP was administered while the patient was receiving ECMO support, yielding a favorable response. The subsequent cycles were conducted without the need for ECMO assistance. The respiratory failure experienced by the patient was attributed to the ALCL disease and was reversible through chemotherapy. By initiating chemotherapy while the patient was on ECMO support, the progression of the disease could be halted, leading to the recovery of respiratory function and discontinuation of ventilatory support enabled by ECMO.

The patient underwent decannulation without any complications following the CHOEP or BRESHAP regimens while receiving ECMO support. This outcome further supports the effectiveness and value of ECMO in treating patients in similar circumstances.

While active cancer has traditionally been regarded as a contraindication for ECMO procedures, the severity of this patient's condition required this particular intervention. Fortunately, favorable outcomes were achieved following chemotherapy cycles while the patient was receiving ECMO support.

In summary, we present a case report of a young adult diagnosed with a histological variant of ALCL who experienced favorable outcomes through the concurrent utilization of ECMO and chemotherapy. This treatment regimen was used whenever necessary while the patient was hospitalized, according to the evolution and overall progression of the patient's disease. ECMO support assumed the role of the patient's lungs during the cycles of chemotherapy. With the ARDS resolved, respiratory function gradually improved, reaching a point where ECMO ventilation could be safely discontinued.

It is important to highlight the critical role played by ventilatory support as demonstrated in this case. Specifically, the initial implementation of ECMO facilitated the execution of comprehensive diagnostic procedures, providing sufficient time to obtain a precise pathology report. Additionally, the life-sustaining function of ECMO allowed the initiation of treatment, monitoring and support for the patient's response. Further, the second instance of ECMO proved to be invaluable by facilitating the administration of the second treatment of chemotherapy, with the goal of potentially ameliorating the pulmonary complications and the lung impairment experienced by the patient.

Given the limited treatment options due to the patient's chemorefractory response, the combination of BV and Crizotinib emerged as a viable alternative for maintenance therapy at that stage.

Unfortunately, the disease advanced during the maintenance treatment, resulting in the development of multiorgan failure and, ultimately, culminating in the patient's death.

This clinical report demonstrates that each case, among numerous others, has not only diagnostic and therapeutic challenges but also needs that should be considered for an adaptable treatment plan based on the patient's disease stage and progression.

Furthermore, it is useful to highlight the importance of a multidisciplinary team approach in the management of each patient, guaranteeing accurate diagnosis and optimal treatment decisions that yield the best possible patient outcomes. This is particularly significant when initial therapeutic proposals need to be adapted and adjusted throughout the course of the patient's treatment.



Chapter IV

Conclusion

Anaplastic large T-cell lymphoma is an aggressive Non-Hodgkin Lymphoma mostly present in children and patients younger than 30 years old. Small cell variant is a rare ALCL histological subgroup characterized by an unfavorable prognosis.

The sinusoidal growth and perivascular distribution pattern observed in ALCL leads to a pulmonary infiltrates, which can induce the development of acute respiratory distress syndrome. It is well established that ARDS is considered as the primary indication for the utilization of ECMO.

Hemorrhagic and thrombotic events, acute renal, multiorgan failure, infection and sepsis are the most frequent complications of ECMO support, representing a higher risk specially in patients with immunosuppression condition or HM. Therefore, the eligibility of patients with HM for ECMO support has been a subject of controversy and has been extensively explored in various studies.

ALCL encompasses a spectrum of mature T-cell malignancies extensively studied in the last years. While certain contraindications regarding the use of ECMO support for patients with HM such as ALCL have been identified, there is growing evidence supporting the benefits of this technique in cases of ALCL-associated acute respiratory distress syndrome (ARDS). Infection control practices are crucial and should be followed meticulously to prevent sepsis in ECMO.

Here, we present a case report of a 19-year-old male diagnosed with S-ALCL. The patient received simultaneous ECMO ventilation and chemotherapy until disease control was achieved, leading to subsequent improvement and resolution of respiratory failure, previously caused by pulmonary involvement associated with ALCL.

In this context, although the patient ultimately succumbed to disease progression, we were able to conclude that certain patients can benefit from ECMO as a transitional support and a “bridge” to chemotherapy. ECMO allows the necessary time to conduct a detailed and well-knowledgeable diagnostic procedure, as well as administer disease-modifying treatments, ensuring the integrity of the lymphoma treatment plan and optimizing patient outcomes. This particular case demonstrates the benefits of ventilatory support provided by ECMO, with no complications after the discontinuation of oxygen supply, supporting the literature.

New treatment strategies are continuously emerging to address the existing gaps in this field. Notable advancements in immunotherapy have been achieved and

targeting specific molecules have demonstrated favorable outcomes. However, the persistence of challenges such as high costs, unpredictable efficacy, potential side effects and the development of resistance hinder the widespread implementation of these treatments. Additionally, conducting robust phase III clinical trials with representative samples remains a significant challenge, particularly for rare diseases such as ALCL.

Furthermore, other investigations should also be carried out in the next few years, namely regarding the benefit of doing HDC/ASCT, given the remaining inconsistent and unclear outcomes yet to be clarified, which highlight the importance of understanding their efficacy and determine their clinical implications.

It is, therefore, imperative to make efforts to overcome these barriers and promote new and promising strategies for these patients, especially in cases where conventional first and second-line treatments have proven unsuccessful and there are no available maintenance or rescue therapeutic options.

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