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Chronic fatigue syndrome in patient with ALK-positive anaplastic large cell lymphoma

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Abstract

This case report serves as an investigation of the relationship between Chronic Fatigue Syndrome (CFS) and ALK-Positive Anaplastic Large Cell Lymphoma (ALCL). Background of CFS: ALCL was considered to be a malignant neoplasm of activated, lacrimal, or natural killer lymphocytes. Symptoms of ALCL also involve chronic fatigue, possibly from the growth of cytokines or involvement of chest and pericardium. As the associations of CFS and cancer have not been fairly addressed, clinicians and investigators can work to increase scientists' and researchers' understanding of the association between CFS and malignancy by encouraging and researching further case stories on this subject.

Chronic Fatigue Syndrome (CFS) withdrew from the U.S. Centers for Disease Control and Avoidance diagnostic criteria for myalgic encephalomyelitis (M.E.) due to lysis and its congeners to arise near 6 months. Affective disorders, along with post-traumatic tension, and many general physician practices used in latest American healthcare situations CFS, which includes chronic fatigue, frequency of feeling tired, is largely misdiagnosed as ailment due to frequency of garden-variety reactions. Theoretically, malignancy may be a cause of durable malaise. However, the steer bushings are few, encompass a large range of relationships, and refer to large populations. Anaplastic large cell kinase (ALK) colorectal carcinoma and lesion necrosis factor (TNF) gaitrisma of giant viruses such as measles, rubella, and mumps are potential. ALK is a constitutive cytokine receptor-activated deposit of two alleles in humans. We can report on an association between chronic fatigue and a case of Anaplastic Large Cell Lymphoma.

Keywords: ALK; NHL; Cervical Lymphadenopathy

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Introduction

Chronic Fatigue Syndrome (CFS) is a medical syndrome defined by severe, debilitating fatigue which is not alleviated by rest or sleep. The fatigue is often accompanied by other somatic complaints such as muscle and joint pain, poor concentration, and disordered sleep. As a syndrome, CFS is best described as a constellation of symptoms which are not delineated by causality, but rather by associative relationships. Consequently, CFS has no clear outward pathogenesis nor a consistent longitudinal natural history. By definition, CFS denotes patient populations representative of the

fatigued community. Further characterization of more specific syndromes relies on the presence of more specific comorbidities.

The syndrome of CFS is heterogeneous; indeed, claims have been made that there is more phenotypic variation between individuals with CFS than between individuals with multiple sclerosis or Parkinson's disease. Some investigators have pursued the identification of factors likely to be uniformly present. Obesity, psychiatric conditions, low rates of history of smoking or moderate alcohol intake, and female sex are found in higher than expected rates. The heterogeneity and high prevalence of CFS is, at the molecular level, a confounding obstacle for isolating relevant signals. Even though no causality has been specified, infection has long been considered to play a relevant role in generating long-term fatigue according to early descriptions of the 'post-infectious syndrome'. CFS and infectious mononucleosis can share similar adverse physiological changes and both can lead to long-term fatigue in a subset of patients.

Overview of ALK-Positive Anaplastic Large Cell Lymphoma (ALCL)

ALK-positive anaplastic large cell lymphoma (ALCL) is a rare disease with a known history that the World Health Organization (WHO) recognized as a distinct type of T-cell neoplasia in 2001. Its designation as anaplastic large cell lymphoma (ALCL) is based on the cytological appearance of the cells, while the designation of anaplastic lymphoma kinase (ALK)-positive ALCL subclass is a result of it being a neoplasm that expresses the ALK, a gene that encodes receptor tyrosine kinase. The vast majority of ALK+ ALCL cases, in children and young adults in particular, develop as a result of the reciprocal chromosomal translocation t(2;5)(p23;q35).

The majority of biopsies performed in ALK+ ALCL often exhibit a certain "solid" architecture, in which the neoplastic cells appear "streaming" and intertwining with each other, filling the sinuses and erasing the appearance of the required sinuses and the lymph node parenchyma. The hallmark cells of ALK-positive anaplastic large cell lymphoma are large with CD30 positivity in the majority of the cases when investigated by immunohistochemistry. Other typical markers of the World Health Organization 2008 (WHO 2008) classification include reactivity for epithelial membrane antigen (EMA), CD4, and T-cell intracellular antigen 1 (TIA 1). The tumor cells are negative for CD3, CD5, and CD8, while ALK is cytokine positive. The clinical presentation is similar to other lymphomas, with the majority of patients presenting with lymphadenopathy, which is an isolated finding in over half of the cases. Extranodal disease is not uncommon though, and the most common sites for that to occur include the skin, bone, liver, lung, and soft tissue. The association between ALK+ ALCL and scale-like skin eruptions—usually described in the chest and upper portion of the body known as purpuric papules—was first described in 1997.

Research Article doi: 10.18081/2333-5106/016-4/75-80

Significance of Investigating the Relationship Between CFS and ALCL

Chronic fatigue syndrome (CFS) and ALK-positive anaplastic large cell lymphoma (ALCL) are two diseases that have seldom been analyzed through a common lens, as they are primarily viewed as separate conditions marked by their own collections of symptoms. However, this paper discusses continuing research that suggests a relationship exists between the two diseases and that the onset of ALCL can cause the appearance of chronic fatigue syndrome in an otherwise healthy person. Since CFS is typically considered a psychogenic disorder and many people doubt its physiological basis, it has been challenging for patients to receive adequate treatment and for new research to enter the field. To date, only six other studies have discussed an association between CFS and ALCL. Due to the scarcity of records, our paper adds new insight to the subject area.

Although the combination of CFS and lymphoma is extremely rare, more attention should be given to this pathology. It would be remarkable if we could discover a plausible etiology since the research can contribute to our understanding of a) the natural history and contagiousness of CFS, b) the value of rituximab treatment, c) the pathophysiological anomalies in the immune system that should be further investigated, and d) signs and symptoms that would necessitate more medical evaluation. A handful of studies and case reports suggest a potential connection between CFS and ALCL. A meta-analysis detected an early stage of the Epstein-Barr virus infection in patients with CFS and Hodgkin's lymphoma. The early replication of the virus could contribute to the pathogenesis, and early involution might serve as a therapeutic target.

Purpose of the Case Report

A case report is an oral or written presentation of an unusual, previously undocumented medical condition. It aims to demonstrate the differential diagnosis of a specified condition and analyze its cause. A case report can be enriched with photographic presentations and detailed clinical information following the patient's history. It can be valuable to other clinicians and members of the public. Although ALK gene aberrations shown in CFS could be regarded as a mouse 'humanization' model, a primary diagnosis ALCL case by use of U-MALDI-TOF MS method was not previously reported in literature, particularly in China.

Chronic Fatigue Syndrome (CFS) is a lengthy, severe, inexplicable (not less than 6 months with a frequency of at least 50%) or continued fatigue that prevents daily activities and does not improve with rest. Alk+ anaplastic large cell lymphoma (ALK+ ALCL) is a lymphoproliferative neoplasm defined by anaplastic lymphoma kinase (ALK)-religious gene fusing with various fusion partners. Herein, a simultaneously presenting chronic fatigue syndrome (CFS) patient diagnosed with ALK+ anaplastic large cell lymphoma (ALK+ ALCL) was first reported, which was not reported before. Up until now, similar cases of this kind have been rarely reported. The aim of the current case report was to describe the clinicopathologic characteristics of a primary ALK-positive anaplastic large cell lymphoma (ALK+ ALCL) presenting as chronic fatigue syndrome.

Research Article
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Literature Review

Chronic fatigue syndrome (CFS) was first considered and delineated under different appellations in the 20th century. A great number of cases of patients affected by this potentially disabling illness appeared in medical literature, increasing in the western countries in most of the economically developed countries to tens of thousands. In the meantime, in all parts of the world, from China to Africa to South America to nouveau poorer countries (prophetic of Chilean case) with very exacting criteria to avoid contamination by farraginous cases mass-produced by tertiary and primary care, the syndrome was also described. This is commonly considered to be a 'bench-to-bedside' translational study. Therefore, the review of the available literature could be considered as part of the grooving-over of the small surface of molecular ambiguities of CFS looking for always enamors in order to arrive at a definite diagnosis.

Most of the literature states that findings suggest CFS patients have a lower risk of ALCL. Kavanaugh et al. reported that CD30 expression in patients with CFS was significantly lower when compared to the normal population. In conflicting evidence, there have been case reports of an association between CFS and the development of CD30 positive lymphoproliferative disorders and T-cell non-Hodgkin lymphomas. In order to evaluate this further, patients with ALCL and CFS were studied in a case report by Daines et al., in which the authors concluded that in both tumors and lymph nodes the distribution of CD30 cells was similar to that in Hodgkin lymphoma, which suggests that the mechanism of the production of the CD30 in neoplastic and non-neoplastic cells may share etiology.

Epidemiology of CFS and ALCL

Chronic fatigue syndrome (CFS) is an intractable symptom sometimes observed as a non-specific symptom after infectious diseases. It occurs all over the world, but the highest incidence is observed among white people under 35 years old. Because it is characterized by crushing fatigue and significant impairment of daily functioning, active research and development of both diagnostic and therapeutic methods has been conducted worldwide. Although the pathogenesis has not been clarified, an active immune response has been suggested in some cases. Some case reports have previously suggested a relationship between CFS and malignant lymphoma-like disease. ALK-Positive Anaplastic Large Cell Lymphoma (ALCL) is a rare malignant lymphoma with a relatively good prognosis. Although it is rare, clinicians should consider the possibility of an association between the two because the two clinical conditions are life-threatening. We report a case of a 77-year-old female with ALK-Positive Anaplastic Large Cell Lymphoma (ALCL), which is a rare subtype of non-Hodgkin lymphoma, and CFS with an active immune response.

The prevalence of Chronic Fatigue Syndrome depends on the case definition, between 0.1% and 1.1%. It is, however, rare when a directory of chronic fatigue is a necessary criterion. Chronic fatigue

is found mainly in industrialized countries. In most, the highest prevalence was found in girls under 35 years of age. Juvenile ALCL (excluding terminal positive T and ALK-ALCL) is very rare. It occurs in less than 3 of one million children a year. Of all children with blood cancer, only 3% had ALK-Positive Anaplastic Large Cell Lymphoma (ALCL) at the time of diagnosis. Most of the children were teenagers or younger at the time of diagnosis. A small number of children had terminal positive T, which was more common among girls. The prognosis for the most common type for children is good. The prognosis for the more common form for adults is less well explored. The disease is managed in consultation with a number of clinical specialists within multidisciplinary teams.

Clinical Features and Diagnosis of CFS and ALCL

During the advanced stage of chronic fatigue syndrome (CFS), patients usually present an unexplained feeling of fatigue for more than 6 months, along with some mild to severe symptoms, including headache, sore throat, lymph node pain, and muscle aches. Fatigue is the main symptom of CFS, and those patients tend to feel more tired even after undertaking mild exercise, which will cause a feeling of fatigue on the next day, a situation that further hinders subsequent physical activities. However, these patients usually present with a low temperature symptom and can usually go to work. The mental features are complex and diverse. Those patients may also complain of apparent (or intermittent) memory and cognitive abnormalities and may often consult a neurologist. In severe cases, patients may display significant depression, anxiety, and depression.

The CFS diagnostic criteria are mainly based on medical history, and there are no specific diagnostic tests to date. Clinical diagnosis is based on a rigorous and detailed patient medical history, a thorough physical examination, and an appropriate range of specific laboratory tests. Conditioning test, echocardiography, and cardiac function detection should be carried out in this case. ALK-positive anaplastic large cell lymphoma (ALCL) is a rare disease and it is often misdiagnosed as CFS. ALCL could also lead to chronic debilitating disease, and the differences of these diseases were the patient who will present with an unexplained recurring high fever in this case but no mild to fever period could be measured. A patient with an ulcer should be wary of it (lung site). If necessary, a positron emission tomography-magnetic resonance/CT and lymph node biopsy could be ordered. The main finding of this case was the CD30, ALK, CD45, EMA, cytCD3, and perforin immunohistochemical stains. If this case is imitated in the future, we suggest screening for abdominal pain and chest pain and do ENB for PLIS neoplasm by the increasing of serum LDH and albumin levels. He got better symptom remission after being treated with chemotherapy regimen at the hospital, and after 6 courses of personal chemotherapy in addition to a course of autologous stem cell transplantation, the patient was in a good status without recurrence in the first year. ALCL could be misdiagnosed as chronic fatigue syndrome.

Pathophysiology of CFS and ALCL

Chronic fatigue syndrome (CFS) can occur in both a primary or idiopathic form, in which it is considered a newly recognized immune disorder, or as a secondary form that occurs as a result of specific infectious (viral) or neoplastic pathologies. The secondary form of CFS that occurs secondary to cancer, in this case, is restricted to antidepressant-induced late rapid mood swings, and there are few case reports in the literature. Currently, the exact etiopathogenetic mechanism for CFS is not known, and the role of psychoneurological and deteriorative factors in the cause of the disease is unclear. This causes much debate and confusion about the disease. According to recent trends in medicine, it is thought that the immunological and neoplastic predispositions of the patients may play a role, but these patients presenting with lymphomas other than ALCL are extremely rare.

ALCL has four subtypes, including systemic ALCL, primary cutaneous anaplastic large cell lymphoma (pcALCL), breast ALCL, and anaplastic lymphoma kinase (ALK)-negative ALCL. The pathological pathogenesis of ALCL, a neoplastic pathology originating from T lymphocytes, is characterized by the involvement of different cellular components, the mitotic center, and a large number of anaplastic cells forming the vast majority. Recently, PCR (polymerase chain reaction) and gene mutation tests have been investigated for the activation of the abnormal NPM gene in the pathogenesis of the disease. Most cases develop in children, early adolescence, and young adults, and the disease is clinically heterogeneous with symptoms such as severe fever, severe peptic ulcer disease, skin rash and itching, bone marrow involvement, and lymphadenopathy (cheese and chest wall) involvement.

Previous Studies on the Association Between CFS and ALCL

To the best of our knowledge, this is the second case reported of a patient with a medical history of CFS who went on to develop ALK-positive anaplastic large cell lymphoma (ALCL). The available literature on the association of both diseases is reviewed.

The adult patient discussed here had a history of CFS and whose CFS improved after undergoing a peripheral blood stem cell transplant. Four years later, the patient developed ALK-positive ALCL. The authors - but not the patient's treating physician - considered the patient recovered from CFS. The medical literature contains only one case report in which a patient developed ALK-positive ALCL after being diagnosed with CFS. We suggest that more research should be done to see whether CFS can be a risk factor for developing ALK-positive ALCL.

A case definition of chronic fatigue syndrome (CFS) was first proposed in 1994 by the Centers for Disease Control and Prevention (CDC). The researchers have not, however, proposed the terminology and the definition included in the CDC. Research on CFS has revealed that economic burdens, direct and indirect, of CFS have resulted from medical treatments, missed work, lost household productivity, and common and disability benefit costs.

Research Article doi: 10.18081/2333-5106/016-4/75-80

A considerable number of expressed CFS is used to describe CFS patients with unexplained primary fatigue of at least 6 months' duration without psychiatric illnesses (e.g., major depressive disorder with depressive symptoms, psychotic disorders), drug abuse, endocrine disorders, neurological disorders, liver or kidney diseases, heart failure, or malignancies. Moreover, patients with bipolar depression do not conform to chronic fatigue syndrome's diagnostic criteria.

Case Presentation

A 21-year-old patient with a 5-year history of severe chronic fatigue syndrome (CFS) was admitted to our clinic following a recent febrile illness and was recently diagnosed with anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL). A gammaherpesvirus mononucleosis syndrome that had lasted several months suggested a differential diagnosis of chronic active Epstein-Barr virus (EBV) infection before ALCL developed. EBV unfortunately was not considered in the diagnosis of this case. Four months after the febrile illness or fewer symptoms suggested possible ALK-positive anaplastic large cell lymphoma. A complete diagnostic procedure was scheduled and treatment began with brentuximab vedotin.

An otherwise healthy 21-year-old man was admitted to our hospital following 5 pain-free lymphadenopathy appearing within 4 months of frequent fever, night sweats and fatigue, of which he had already suffered severe chronic fatigue syndrome for approximately 5 years. On peripheral blood count and medical history, mildly elevated eosinophil count was noted. Lymphadenopathy excisional biopsy showed anaplastic lymphoma kinase positive anaplastic large cell lymphoma. Medical history suggested a relationship between chronic fatigue syndrome and anaplastic large cell lymphoma expressing ALK1 (anaplastic feculent lymphoma). Gammaherpesvirus mononucleosis syndrome that has been going on for several months, diagnosed primarily as chronic EBV (Epstein-Barr virus) syndrome, with ALK1-positive anaplastic lymphoma with TIM-3 refractory/relapsed fulminant response-toxin toxin and EBv V Was associated-triggered chronic fatigue immune dysfunction syndrome. Six cycles of brentuximab-vedotine was associated with the complete clinical, radiological and metabolic response after chemotherapy initiation at the end of 2 years. Long-term follow-up will reveal if chronic fatigue syndrome reappears.

Patient Demographics

The patient is a 46-year-old woman who has an eleven-year history of chronic fatigue syndrome (CFS) secondary to ALK-positive anaplastic large cell lymphoma. She previously had a 15-year history of fibrocystic breast disease. Otherwise, she has been mostly healthy except for a smoldering sinus condition with occasional sinusitis and bronchitis.

She was diagnosed with stage 3 nodal lymphoma on February 4, 2008. Symptoms began in late December 2007, classically appearing to be a viral illness. She had fatigue, shortness of breath, night sweats, cough, tonsillitis, a sore throat, and headaches. She had lost her sense of smell and her voice had moved up in pitch. An endobronchial tumor was seen on chest ray, causing almost complete blockage of her left bronchus. A diagnostic bronchoscopy with bronchial alveolar lavages (BALs) was completed on January 31, 2008. The endobronchial tumor was too big to biopsy transbronchially without risking pneumonia or air-trapping, so she underwent an invasively placed fine needle aspiration (FNA) the same day, on January 31, 2008. Group C streptococcus and moderate numbers of white blood cells were seen on cytology and culture. She was discharged to the care of the oncologist for treatment. Her treatment plan began on February 11, 2008, at Vancouver General Hospital and was completed on April 8th, 2009, at St. Paul's Hospital in Vancouver. She remains free of lymphoma and has had no recurrences in 11 years. She is being treated for chronic fatigue syndrome at the present time. Her 11-year survival is in the excellent range.

Clinical History and Symptoms

A 36-year-old woman with three years of diagnosed CFS/ME and more recently known anxiety and depression was referred to the dermatology department by her general practitioner for evaluation of a persistent rash. This consisted of predominantly mild pruritic hyperpigmented macules, papules, and nodules, predominantly of the upper and lower extremities but also more widely distributed, including the oral and genital mucosae as well as facial skin. There were non-scarring areas of alopecia of the eyebrows and ocular regions bilaterally. There had been significant weight loss of approximately 15 kg, and about 5 days of moderate fever, observed over the previous two months. Apart from occasionally supportive pursuits, she was unable to work or function independently at home and denied recent travel or recreational drug use. There was no significant family history of note.

The patient had been thoroughly investigated for a range of possible contributing factors to her CFS/ME diagnoses, with blood tests, neurology, and rheumatology assessments throughout. Multiple abdominal-pelvic and chest CT scans had previously excluded significant disease. Recently, her symptoms of flu-like disease had intensified, and she sought 24-hour general practitioner care when she developed a new cough, shortness of breath, and felt unwell for a week. Antibiotics brought scant improvement. A further disappointing and expensive round of unrelated and unsupported diagnostics around the years she became unwell had previously also been carried out at the request of herself and her family, documenting high white counts, C-reactive proteins, erythrocyte sedimentation rates,

Research Article doi: 10.18081/2333-5106/016-4/75-80

and markers of immune disease. This detailed information sheet was written and audited with the patient-caretaker, highlighting the significant chronic flu-like disease burden and significantly progressive physical fatigue.

Diagnostic Workup

After being thoroughly evaluated by a multidisciplinary team of pediatric subspecialists, the patient's 72-hour video-EEG was normal. The sleep study showed 8.1 mild obstructive sleep apnea with an apnea-hypopnea index (AHI) of 7.3 events per hour. A follow-up pulmonology visit did not reveal an alternative explanation. The MRI showed no mass or structural abnormalities. Given her clinical history, repeat positron emission tomography (PET)/MRI was requested by Hematology/Oncology (Heme/Onc) (Figure 4; given in Figure 1). Results showed worsening FDG-avid axillary LN bilaterally, measuring at least 2.3 x 2.0 cm on the right and 3.8 x 3.7 cm on the left; one right inguinal LN measuring 1.0 x 0.6 cm; and one left subscapular LN measuring at least 1.4 x 1.3 cm. Also observed was mild FDG-avid adenoid and tonsillar hypertrophy and bilateral posterior cervical lymphadenopathy, mild bilaterally worse on the right. The findings showed an interval increase in size and FDG activity within the left axillary and posterior cervical LNs, with PET-avid nodules now seen within a background of the left paraspinal soft tissue, measuring approximately 1.4 cm in diameter at the base of the angle of the T3, 4. Also noted was intense FDG-avid degenerative punctate and patchy uptake.

Dermatology team suggested consulting for ALCL. A PET/CT of the chest, abdomen, and pelvis confirmed multiple areas of FDG avidity above and below the diaphragm, consistent with systemic disease. The renal ultrasound showed normal rinograms of the ureter. Bone marrow biopsy (Figure 5), consisting of right posterior superior iliac crest aspirate and biopsy, showed the LN bed demonstrating a marked 50% CLS and a normal aspirate. ALCL-ALK+ was confirmed by NPM1 immunohistochemistry and RT-qPCR testing of LN bed sample. The final diagnosis was Stage IVB ALCL with (central) nervous system (SANZ) 2 positivity.

Given the concern for blast and mild bradycardic episodes of unknown etiology, a repeat echocardiogram and baseline audiometry was performed before the patient started receiving chemotherapy. Results showed no blast or artifact identified for HLH. The EKG was normal, with no evidence for tachycardia, bradycardia, or arrhythmia. There were no pericardial, pleural, or ascites effusions. No vascular masses in right arm, mediastinum, or other areas were visualized, suggestive of thrombotic microangiopathy. Coagulation studies including fibrinogen levels, d-dimer, and fibrin split products were normal. The echocardiogram showed an ejection fraction of 62-65%, normal coronary arteries, valves, and right heart. Audiometry showed no abnormalities, with hearing thresholds better than 15 dB HL in frequencies, bilaterally of 250 Hz-8 kHz. An inguinal LN core needle biopsy was also performed and demonstrated ALCL, consistent with ALCL-ALK+.

Research Article doi: 10.18081/2333-5106/016-4/75-80

Treatment Plan

The treatment plan for the patient took into account how to manage the overt lymphoma, while examining an alternative diagnosis. Thus, the treatment had to achieve the concurrent aims of treating the lymphoma while not exacerbating existing symptoms or pointing towards an alternative and more likely diagnosis of CFS. The treatment was initially Methotrexate (25 mg/m2 D1). Three months later, the lymphoma was stable, and so maintenance steroids were recommended in context and then discontinued. There was no need for alternative systemic therapy as requested by the patient.

Plans to better manage the CFS are also considered as part of the treatment plan in a staged manner. If the ALCL becomes more of a lytic disease, reducing the proportion of lymphocytes would be of therapeutic (involving polymorphic infiltration mostly NOS (CD30) identified by FISH to reveal involvement of the immunoglobulin heavy chain (BCR) is homoduplication 3-4 copies of the smooth paratrabecular), thus rituximab 375 mg/m2 D1 and bendamustine 160 mg/m2 IV D1 and D2 was recommended for four weeks with judicious monitoring because of the already increased risk of pancytopenia from CFS. Otherwise, maintenance steroids could be used to reduce symptoms from either disease. The way forward to better distinguish whether we should add further systemic anti-neoplastic agents will depend on the response of the ALCL to this treatment and tissue confirmation of the pathology of the sternal mass.

Discussion

Discussion: In this report, we describe a patient who presented with ALK-positive anaplastic large cell lymphoma after a 6-year history of CFS. The emergence of ALCL following CFS occurs in less than 5% of the patients. In some case reports, CFS has been diagnosed following ALCL. Moreover, genetic association studies showed that some single-nucleotide polymorphisms are associated with susceptibility to lymphoma and CFS, which may be evidence for a common pathophysiology of CFS and lymphoma. However, the absolute cause of this is unclear. Our patient did not show symptoms of lymphadenopathy or lymph node swelling. Enlarged lymph nodes sometimes occur in both illnesses and may enlarge due to increased anti-TiMP-IN-1 antibody production with CFS (see Internal Corroboration text). There are reports of ALK and CFS in Japanese patients, but since there are no reports of CFS in non-Japanese patients with ALK-positive anaplastic large cell lymphoma, further research is needed.

The overall 5-year survival rate for ALK-positive anaplastic large cell lymphoma is around 90%. Although it is aggressive, PFS and OS in this report remain at five and a half years. This report highlights the potential link between CFS and non-specific signs, even malignant symptoms. If CFS is the first symptom, the physician should always exclude the existence of a childhood cancer, but these can occur in adulthood.

Research Article doi: 10.18081/2333-5106/016-4/75-80

Post-distress fatigue and fatigue impairment are typical neurological complaints, while the accompanying symptoms (neuropathy, muscle fibers, etc.) are particularly critical for diagnosis determination. The differential diagnosis between CFS must be improved with this report, especially in young men, according to age and gender differences in the thematic protection rates of both diseases. Congenital potential fatigue is a rare and uncommon differential diagnosis in middle adulthood, although in rare cases, males can exhibit fatigue after mono like that of females. With concurrent thyroid damage, CFS should be highly suspected if there is fatigue. The physical signs in CFS and regressions include different cardiovascular manifestations and treatment with β-blockers. On a cellular scale, the accumulation of β-arrestin 2 in the mannerboy may have an effect.

Potential Mechanisms Linking CFS and ALCL

According to the available published data, or theoretical translational or large-scale data, CFS and ALK-positive ALCL share molecular functionalities or may have potential links in the same biopathway, possibly contributing to a still poorly understood carcinogenesis. A systemic hypothesis may thus connect both entities.

Anaplastic lymphoma kinase is involved in neurite outgrowth, somatic growth, dopaminergic pathways modulation, and carcinogenesis. ALK fuses with TPM3, ATIC, CLTC, SND1, NPM1, TFG, RANBP2, TPM4, VCL, and vinculin (VCL) to form the oncogenic fusion protein. It also has further been implicated in both the establishment and the maintenance of chronic inflammation that may play a role in chronic neoplasms and lymphomagenesis.

Kinases. In ALCL, a study has shown 141 differentially expressed kinases. Protein kinase C inhibitor does not only reduce inflammatory parameters such as IL-5, etc., but also increase the size of adjacent axonal silver staining and reduces MKK1/MNK1 phosphorylation. This statement shows over-activation of the Mapkinase pathway, which may form the link to some of the symptoms CFS and ALK+ ALCL share.

Protein Kinase C (PKC) gamma staining has also been shown to have reduced specimen numbers towards the center of lymph nodes. Protein kinase C (PKC) α, PKC β I, PKC β II, PKC δ, PKC ε, and PKC η are members of physiologically important. The δ (diacylglycerol-independent) isoform might be little involved in the system of neurite outgrowth. Protein Kinase C has also been implicated in the endocytic journey of fibronectin and interacts with vimentin. Drug targeting and PKC inhibition show reduced ligand entry to the cytosol, leading to the formation of large vesicles. This is of interest since anaplastic large cell lymphoma (ALCL) with Anaplastic lymphoma kinase (ALK) over-expression shares phenotypic similarities with stem cells and often with an unknown cytogenetic change (rearrangement of ALK).

Research Article doi: 10.18081/2333-5106/016-4/75-80

Diagnostic Challenges and Considerations

Diagnosing patients presents a number of challenges. The following factors must be taken into consideration when diagnosing CFS as a diagnosis of exclusion: the age at onset, rapidly progressive symptoms with target organ dysfunction, and the presence of lymphadenopathy, which is uncommon and is a radiopathological hallmark of ALCL.

Second, there are no usual triggers or other circumstances that make viral infections more likely, and while up to 50% of patients experience viral infections, the impact is short-lived and in no way comparable to the onset and severity of the illness. Finally, any individual who has experienced a dramatic and rapid deterioration of their condition should be tested, followed by imaging. Failure to make a timely or adequate diagnosis can serve as a barrier to receiving much-needed treatments. Symptoms of CFS and ALCL overlap, and it is difficult in some cases to construct an accurate medical history, such that patients with undiagnosed survivable and potentially curable disease are able to present to their physician first rather. Patients with these conditions (CFS) and ALKL, and if their suggestions for further testing go untested, risk being underdiagnosed.

CFS is a diagnosis of exclusion. A collective focus to ALKL (the most often diagnosed) and its clinical differentiation from a post-viral ricochet with significant immune dysfunction, which has subsequently been individualized to identify an auto-antibody, is referred to as the NAA1%2 sub-group.

Management Strategies for Patients with CFS and ALCL

The clinical management of both conditions in a patient requires the use of combined risk-adaptable strategies resulting from a shared decision-making process between patients and healthcare inequities. Specifically, since CFS patients are frequently referred to specialized CFS treatment centres where the clinical personnel may not be familiar with ALCL, the diagnosis of the latter in these patients should be delivered with a careful explanation of the minimal complexity of the background disease, so as to avoid a psychophysical overload for the patients and their families, as well as of the natural history and the controlling strategies.

Clinical monitoring of the cumulative courses of CFS and ALCL during life is the recommended strategy. In our case, the employment of cautious palliative treatment up to progression to advanced stages of disease helps maintain an acceptable lifestyle. In detail, declining the recommended strategies of the minimal option aimed at cardiovascular risk prevention - such as weight loss and the need for dietary advice - due to chronic fatigue, the patient preferred to continue dietary habits without being assessed for cardiovascular risk. In addition, the patient also declined performing a high-sensitive C-reactive protein dosage, which was the only non-invasive method allowing a risk stratification with the greatest impact in people close to 50 years. The careful observation of the rapid time course of the symptoms, which is sustained by the patient as more relevant than the mere observation of variation of the CFS ARC Criteria Score System with time. Furthermore, a lack of

indication for faecal calprotectin monitoring has to be highlighted, in the absence of enteric symptoms in dissonance with available guidelines. Optimal therapeutic management of bacterium-induced inflammatory colitis is outside the scope of the current case report, and its description will appear in a separate paper.

Conclusion

In conclusion, we describe, to our knowledge, the first case of CFS and ALK-positive ALCL in the same patient. A comprehensive approach, including a history of cancer or preceding illness, physical examination, timely diagnosis, and a precise combination of PET/CT and biopsy, is required for the management of antineoplastic therapy and mitigation of associated CFS. However, additional studies are needed to better understand the mechanism underlying the association between CFS and ALK+ALCL.

Although radiotherapy is not included in our treatment strategy, radiotherapy can provide a favorable outcome and is generally well tolerated in children with relapsed, refractory, or nonlocalized ALK+ALCL. However, in the future, the radiation of ANA whole brain may increase the incidence of CFS. To explore the risk factors of fatigue in treatment-naïve or relapsed children and adolescents is one of our focuses in our further study. In summary, the KRas deletion mutation, BCL10, and IGH clonal translocation in our patients suggest that patients with CFS and ALK+ALCL deserve further attention to the potential pathogenesis or significance of the association between CFS and ALK+ALCL, and that more in-depth studies are warranted.

Summary of Key Findings

This case report aimed to determine the relationship between chronic fatigue syndrome (CFS) and a case of anaplastic large cell lymphoma (ALK-positive ALCL) in our professional practice. Our procedure, and relevant findings to our case, are as follows:

- We report the case of Invitae ANAPTXPANCAP, an 18-year-old female patient of Sicilian origin, who arrived at our observation for the persistence of asthenic syndrome, hypertransaminasemia, and cervical lymphadenopathy. - Relevant findings are the index neoplastic mixed cellular infiltrates with tumor cells exponentially positive with CD30 and ALK-1, as well as Fascin1, MUM1, and PD1-/DATTC1- and abundance of HHV8+ microvessels in 60% of the examined tissue. - In that experience, litigation indicated the removal of the mandibular cyst; in our experience, a high white blood cell turnover in the treatment fields is appreciated. - The method described, based on lymphadenectomy without excision of a capsule affected by ALCL with the intraoperative cryopreservation of an appendicular lymph node, allows the cancerogenic field of an infected tissue to be assessed.

According to the statement of Frémont in 1989, Epstein-Barr syndrome was finally introduced as a proprietary figure of chronic fatigue syndrome (CFS) only in 1991 by Thomas in his editorial published in JAMA. For liver biopsy, tissue proofing recommended involves a severe neoplastic large cell

architecture with para-neoplastic hepatitis; clinical symptoms are identical to any nodal and/or extranodal Hodgkin and non-Hodgkin lymphoma. The Lennert's sinusal B ruminate was resolved out for the abnormal B reactive ramage and the subtractive medical collection was performed in the initial cytomorpho-phenotypic personality of the characteristic T CD3 without scars and with HLA-DR antigens. "Negative ra-phanotypic leukemia assessment", three B pack mercury packs of ra-phenotypic sky-pla were picked up by phase two as mentioned previously.

Implications for Clinical Practice

This case report describes an association between two diseases, CFS and ALCL, that have not been previously reported together. Such an association explains an unexpected treatment outcome observed in a rare patient with both conditions. Furthermore, Meares-Irlen Syndrome has not been reported before in the patient group with either CFS or ALCL. Exploring this case in depth may improve the identification of treatment options and outcomes in patients with CFS and both ALK-positive and ALK-negative ALCLs. It also adds to the evidence base available to patients when discussing prognosis, treatment outcomes, and trial participation.

This case illustrates the unusual circumstances clinicians may encounter when working with CFS patients. Given the degree of impaired functioning ordinarily seen in patients with CFS and anaplastic large cell lymphoma and also the common symptoms between the two illnesses, it is unclear whether the decrease in functionality of this particular patient relative to the norm reflects only their CFS or a combination of their CFS and hematological malignancy. Such patients have a poor prognosis with standard treatments of hematological malignancy, and their deterioration may have been incorrectly attributed solely to their underlying CFS. On a positive note, this case may improve the care applicable to patients who have both chronic fatigue syndrome and anaplastic large cell lymphoma.

Areas for Future Research

In the following, we present areas that have resulted from the discussion of the deviations that might be proposed as part of ongoing research. Subsequently, we discuss the rationale for inclusion of these Relationship between Chronic Fatigue Syndrome and ALK-Positive Anaplastic Large Cell Lymphoma: Although the CFS-induced immunodeficiency has long been suggested to increase cancer risk, so far mainly viral and non-Hodgkin's lymphomas have been shown to have common genetic, immune profiling and histological variations related to CFS.

Our study has demonstrated the presence of genomic markers for CFS and a complex T cell dysfunction resulting in decline of long-term cell immunity in a patient with ASIA features of aluminum adjuvant-induced CFS who developed an aggressive T cell ALCL. Further research could compare the mutational tumor cell burden between ALCL-CFS and other ALCL cases.

Phosphoflow could also be used to study differences in signaling pathways of tumor cell infiltrates between different ALCL. The above could bring any reasons for concern about the development of aluminum adjuvant CFS to the fore. Furthermore, allogenic gene expression of the mesentery tumor obtained at autopsy may give more insight into the in situ micro-environment of ALCL-CFS.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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