

Case Report: A Woman with Fever, Acute Changes in Mental State, and Progressive Neurological Degeneration

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Abstract

Introduction: Anaplastic large cell lymphoma (ALCL), which was first described by Stein in 1985 as a feature of CD30 positivity, is now acknowledged as a distinct subset of T-cell non-Hodgkin lymphomas (NHL). It accounts for approximately 3% of adult NHL while constitutes as many as 30%–40% of pediatric large-cell lymphomas. It is rarely metastasized to other sites, especially to the central nervous system (CNS).

Case Report: We present a case of a 73-year-old woman hospitalized for fever, acute behavioral changes, and progressive neurological degeneration; a rare case of systemic ALCL which metastasized to the brain. There are very few case reports of this matter in the literature.

Conclusion: In the management of patients with neurological impairment, cognitive, and behavioral changes, we suspect the presence of lymphomas associated with the CNS still suspicious of other primary causes.

Keywords: Anaplastic large-cell lymphoma, anaplastic lymphoma kinase gene, primary central nervous system lymphoma, non-Hodgkin lymphoma, T-cell lymphoma, lymph node enlargement.

Introduction

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL), but one of the more common subtypes of T-cell lymphoma. ALCL comprises about 2% of all NHL and approximately 20% of all T-cell lymphomas [1]. Systemic (ALCL) is a clinically and molecularly heterogeneous type of peripheral T-cell lymphoma and a Rare Group of lymphoid malignancies. It may be sub-divided into cases with or without translocation of the anaplastic lymphoma kinase gene (ALK), leading to overexpression of ALK [2]. ALCL was first recognized based on characteristic histologic features (sinusoidal invasion) and a distinctive immunophenotyping (CD30). However, neither sinusoidal invasion nor CD30-positivity proved to be entirely specific. Subsequently, a characteristic cytogenetic abnormality was identified, the t(12;5), which led to the identification of the genes involved in the most common

translocation of ALCL (NPM/ALK) and insights into the pathogenesis. Generation of monoclonal antibodies to the aberrantly expressed ALCL tyrosine kinase or ALK (ALK-1 and ALKc) can be used diagnostically, and have led to the improved definition of the diagnostic entity with important clinical and prognostic implications [1]. While the outcome for patients with ALK-positive ALCL - particularly in pediatric patients has been very favorable following doxorubicin-based therapy, ALK-negative cases have fared more poorly. Approaches such as autologous transplantation have been studied in this group in an attempt to improve outcome. ALCL has an aggressive natural history but excellent response to combination chemotherapy containing doxorubicin. It is one of the most curable of the aggressive NHL [2]. ALCL is most common in the pediatric, adolescent, and young adult age groups. In some series, bimodal age distribution is seen. However,

cases of ALCL in the elderly usually are t(2;5) or ALK-negative, and probably constitute an unrelated clinicopathologic entity. There is a marked male predominance, up to 6:1 in some series. ALCL usually presents with lymph node enlargement. Frequent extranodal sites of disease include skin, bone, and soft tissue. Involvement of other extranodal sites is less commonly seen. Initial symptoms of ALCL can include fever, backache, painless swelling of lymph nodes, loss of appetite, and tiredness [3]. In general, ALCL of the central nervous system (CNS) has been recognized to be significantly more aggressive compared to systemic ALCL or PCNSL. However, the data demonstrate that ALK-positive ALCL has a good prognosis, similar to systemic ALCL [3]. Tuberculosis (TB) or other infectious diseases of the CNS are often to be suspected. Delayed diagnosis may result in a worse outcome compared to that observed in other ALK-positive patients. An early

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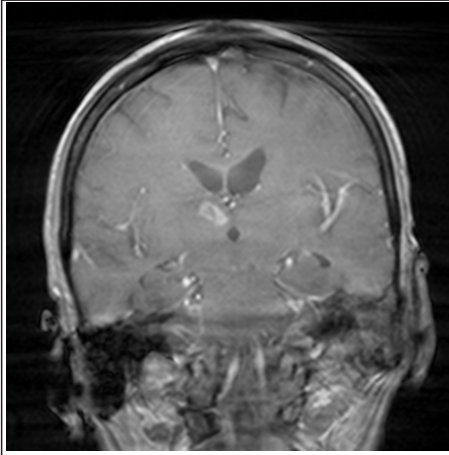


Figure 1: Coronal T1 with gadolinium: Ovoid image with an annular relief in the right thalamus.

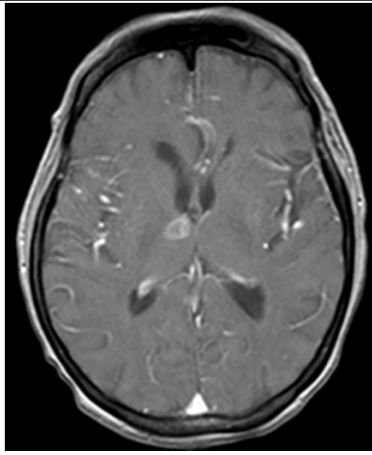


Figure 2: Axial T1 with gadolinium: Ovoid image with an annular relief in the right thalamus.

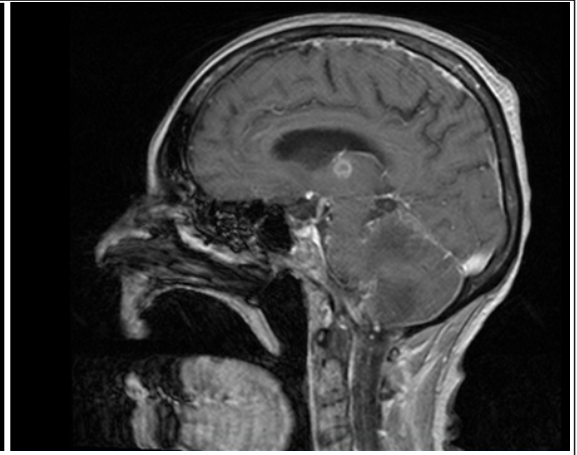


Figure 3: Sagittal T1 with gadolinium: Ovoid image with annular relief in the right thalamus.

diagnosis and the timely initiation of the appropriate treatment is critical [3]. The prognosis of ALCL of the CNS is correlated with ALK positivity and patient age of <40 years. Chemoradiotherapy with MTX is recommended as the standard treatment for ALCL. However, additional multicenter studies including large numbers of cases are required [3].

Clinical Case

A 73-year-old woman was hospitalized for fever, acute behavioral changes, and progressive neurological degeneration (especially on the right side of the body and brain).

Relevant background

Glaucoma with 11 years of progression. Stenosis and aortic insufficiency with a stable regurgitant fraction submitted to valve replacement; post-surgery echocardiograms showed normal function.

1 month before hospitalization she had extreme mood changes treated with the antidepressant escitalopram and previous hospitalization for asthenia, adynamia, somnolence, tachycardia, fever, and hypogastric pain.

Blood test

Albumin 3.31 g/dl (reference 3.97–5.30 g/dl), lactate dehydrogenase 686 U/L (reference 0–480 U/L), sodium 131 mmol/L (reference 135–145 mmol/L), chloride 91.9 mmol/L (reference 98–107 mmol/L), highly sensitive C-reactive protein 149 mg/L (reference 0.060–10.90 mg/L), activated partial thromboplastin time 37 s (witness 30.2 s), and triiodothyronine 0.35 ng/ml (reference 0.80–2.0 ng/ml).

Urinalysis

21–30 leukocytes/field, 16–20 erythrocytes/field, abundant bacteria, and a

moderate quantity of transitory cells.

Other tests

X-ray of thorax apparently was normal. 12-lead electrocardiogram report found only sinus tachycardia. Cranial tomography showed physiological calcification in the basal ganglia, abiotrophic changes in relation to age, maxillary and sphenoidal sinusitis and changes compatible with atherosclerosis. The patient was hospitalized for treatment of an infectious process, probably urinary.

Progression

Urinalysis indicated growth of *Escherichia coli*, treated with ceftriaxone. The patient presented diplopia, peripheral facial paralysis, and mild paralysis of the third right cranial nerve, and reported decreased food consumption. A nasojejunal feeding tube was inserted for endoscopic examination, finding an ulcer >0.6 cm in the

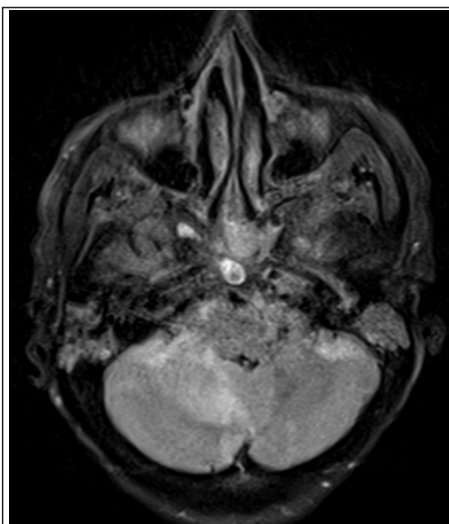


Figure 4: Axial flair with diffuse hyperintensity in both cerebellar hemispheres.

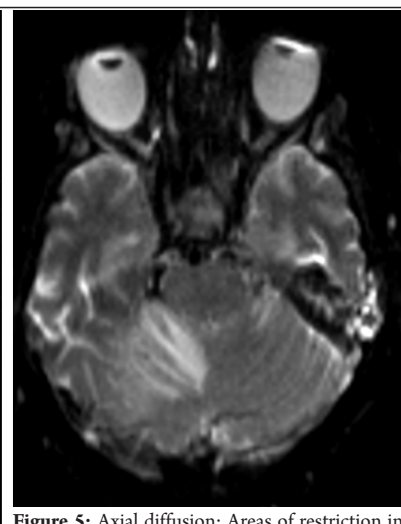


Figure 5: Axial diffusion: Areas of restriction in the right and left cerebellum as well as the right-middle cerebellar peduncle.

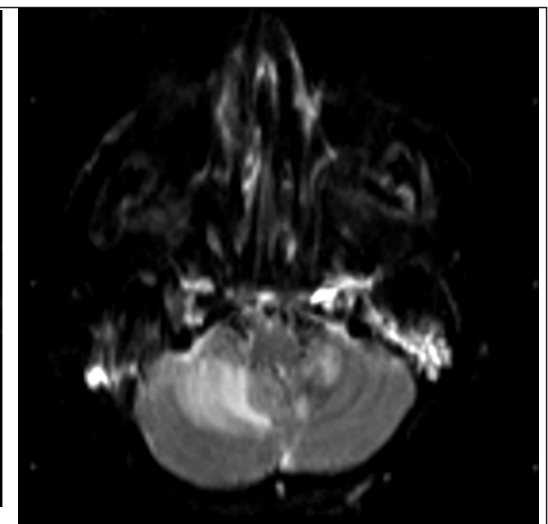


Figure 5: Axial diffusion: Area of restriction in the cerebellar hemispheres.

process of healing. Complete enteral feeding was initiated. Fever persisted. Tonsillitis was ruled out by transthoracic echocardiogram. Sudden decline in alertness accompanied by Raynaud's phenomenon, tachycardia and hypotension refractory to treatment with solutions. Consequently, the patient was treated with amines and an endotracheal tube was inserted. There the blood test showed dimer D 16.42 ug/ml, fibrinogen 5.73 mg/dl, prothrombin time 13.17 s, activated partial thromboplastin time 35 s, INR 1.16 %, hemoglobin 13.1 g/dl, lactate dehydrogenase 899 U/L, and glucose 199 mg/dl. A thorax X-ray indicated bilateral interstitial infiltrate with a patch pattern diagnosed as ARDS. The A DSNET protocol was initiated. New urinalysis was positive for *E. coli*; therefore, antibiotic treatment with ceftriaxone was continued. Up to this point, the acute symptoms appeared to be of infectious origin in the urinary tract and the respiratory decline could be attributed to pulmonary aspiration. The hemodynamic disorders could be attributed to the hypoxemia event. Imaging studies demonstrated a cerebral vascular ischemic event in the right thalamus, cystic tumor in the pancreas tail of unknown origin, and a chronic hemorrhagic process in the right adrenal gland; these symptoms suggested an infarct in the spleen and probable hydrocholecyst. In blood culture *Candida krusei* was detected; amphotericin treatment was initiated. The hydrocholecyst was treated by percutaneous hepatic cholangiography. *Achromobacter xylosoxidans* and *Klebsiella pneumoniae* were isolated from the bronchial secretion. Magnetic resonance imaging showed a diffuse lesion in the cerebellum with amygdalar descent, as well as bilateral otomastoiditis, ethmoid sinus, and predominantly periventricular leukopenia. An annular lesion of the right thalamus was highlighted with the contrast medium. A compressive lesion of the right cerebellar vermis and cerebellum (not corresponding to any vascular region) was shown, as was edema with a subtle displacement to the left of the fourth ventricle, and a paraventricular lesion (Fig. 1, 2, 3, 4, 5, 6). Ovoid images were present in the meninges, the basal cisterns, the ethmoidal and sphenoidal cells, and the petrosal ridge of the temporal bones. The findings suggest neuroinfection and right paraventricular parenchymatous abscess. A spinal tap showed an icteric fluid,

the presence of yeast, low glucose level (42 mg/dl and 438 mg/dl in venous blood), high protein level (438 g/dl), and pleocytosis (42 cells). The patient was treated with amphotericin, meropenem, and vancomycin at meningeal doses. The patient progressed with bilateral mydriasis (pupils at 6 mm), the right eye with dyscoria. The bilateral reduction was found in the size of the optic disc at the back of the eyes; the cough reflex was absent, with the presence of hyperreflexia and clonus. The scheme of amphotericin, meropenem, and vancomycin was continued, adding a systemic steroid.

Differential diagnosis

At this time, the question that arose was whether the infectious processes should be considered as the etiology of the neurological developments, or whether these two processes were interrelated. The approach of analyzing the acute alteration in the mental state was reinitiated, seeking to distinguish between primary and systemic causes by order of frequency and risk factors.

Primary causes

The possibility of a cerebral vascular accident is involved in differential diagnosis of cases with the sudden neurological decline, especially with a patient of advanced age with a likelihood of atherosclerosis (documented by imaging). When the patient arrived at the hospital, the Cincinnati score did not suggest an acute cerebral vascular accident. The imaging carried out did not support such a diagnosis either. However, in abnormally acute cases, cranial tomography is usually not sensitive to identifying infarcts. Its utility is the relatively high sensitivity only in the identification of acute hemorrhaging [4]. There were no alterations in density that could suggest early signs of ischemia [5]. Infectious processes can also be implicated in acute changes in mental state. We found fever and neurological alterations, without clinical evidence of meningism. Relevant signs of meningism are nuchal rigidity, Kernig's sign, and Brudzinski's sign, which translate into a high specificity of up to 95% [6]. The magnetic resonance revealed lesions in the right thalamus that were highlighted with gadolinium and also changes in the leptomeninges. The spinal tap showed a high protein level, low glucose level, and pleocytosis, with a probability of

bacterial meningitis. The focus of the symptoms led to a suspicion of cerebral abscess, although there are contrasting symptoms such as the absence of isolation of bacteria and the lack of response to therapy. The glucose and protein content of the cerebrospinal fluid (with or without pleocytosis) is also indicative of cancer or lymphocytic meningitis, above all in cases of Burkitt's lymphoma or intravascular lymphoma. In the latter cases, the tumor may be cancerous [7].

Systemic causes

The patient was hospitalized with a documented infection accompanied by other clinical abnormalities, inflammatory markers, hemodynamic variables, and an organic or perfusion dysfunction [8]. It is not uncommon to find encephalopathy that is caused by sepsis, above all when it is related to a decrease in alertness and changes in behavior associated with an infectious process. Liver failure was not considered due to the lack of alterations in coagulation and lack of abnormality in the tests of liver function. The disorder detected in relation to alkaline phosphate could be attributed to hydrocholecyst [9]. Regarding the kidney, no increase was found in nitrogen-containing compounds or other markers of acute kidney injury or uremia such as phosphorous, which is known as a marker of the late stages of acute kidney injury. Given the extremely low probability of this type of disorder, tests were not carried out for neutrophil gelatinase-associated lipocalin or cystatin C [10]. Finally, there were no major alterations in thyroid hormones or relation to medications.

Outcome

In the intensive care unit, aggressive treatment was given to combat neuroinfection, support hemodynamics and protect the brain; all carried out under deep sedation. A new magnetic resonance showed the persistence of hernias. The cerebrospinal fluid culture did not show any bacterial or fungi growth because of the lack of response to treatment; it was decided to treat the patient for mycobacteria with a mixture of imipenem, caspofungin, voriconazole, ampicillin, and linezolid, as well as an antituberculosis cocktail (rifampicin, isoniazid, pyrazinamide, and ethambutol). The developments were not

favorable, and the patient died before being able to carry out any surgical procedure, despite the antibiotic treatment and the measures taken to counteract intracranial hypertension.

Autopsy

An autopsy was requested, resulting in a final diagnosis of advanced anaplastic large CD3/CD8 T-cell lymphoma in the lungs, right kidney, right adrenal gland, pancreas, and meninges. Cerebral edema and right parieto-occipital subarachnoid hemorrhage were found, with hernia of cerebellar tonsils, and also were found cardiomegaly with concentric hypertrophy of the left ventricle and saccular dilation of the ascending aorta in the site of the previous surgery.

Discussion

The participation of the lymphomas in the entities related to the CNS, whether primary or secondary, is an unusual complication that has been described in the context of patients with hematologic diseases. Its importance is in regard to the considerable morbidity and mortality. In the United States, the incidence for primary lymphomas of the CNS is approximately 1%

of all primary tumors, based on a large number of autopsies [10]. Cognitive and behavioral changes are the most common symptoms of lymphomas associated with the CNS through the frontal lobe, corpus callosum, and paraventricular structures. In approximately one-third of patients, the lymphoma is multifocal, with neurological deficits [11]. We had received the patient under mechanical ventilation status; this circumstance made impossible to detect infiltrating neurological signs that is why the primary diagnostic suspicion was TB. Clearly, early diagnosis improves the possibility of patient survival. Early diagnosis with magnetic resonance is very limited in patients with hematological neoplasms, although this method is good for detecting participation of leptomeninges (more when secondary to solid tumors than when caused by leukemia or lymphoma) [12]. In general, early diagnosis of meningitis associated with neoplasm depends on the type of tumor. In this particular case, we do not run a blood smear from the beginning because the patient did not present lymphadenopathy, splenomegaly, thymus or some other lymphoid organ enlarger, suggestive

infiltrating skin lesions, bone pain, and systemic manifestations such as fever, sweating, itching, and weight loss. Another study that is required for making a definite and specific diagnosis is an analysis of cerebrospinal fluid in which the protein level and pleocytosis are determined [13]. One of the principal differential diagnoses was bacterial meningitis. However, we found high protein content and pleocytosis in the spinal tap analysis of the patient. Therefore, in future, it would be interesting to use flow cytometry in patients suspected of having some type of meningitis to evaluate the cerebrospinal fluid because this would permit early detection of neoplastic meningitis (even before the symptoms appear). The final diagnosis is lymphocytic meningitis secondary to advanced anaplastic large CD3/CD8 T-cell lymphoma.

Conclusion

In the management of patients with neurological impairment, cognitive and behavioral changes we suspect the presence of lymphomas associated with the CNS still suspicious of other primary causes.

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