NEUROLOGICAL COMPLICATIONS OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

We report a case of a 44 years old female patient diagnosed with acute lymphoblastic leukemia – the proB subtype – with a peculiar evolution of the disease – first three months, with primary fibrinolysis syndrome, marked depression and neurological symptoms. The patient was diagnosed with subarachnoid hemorrhage and leukemic meningoencephalitis, with a good clinical outcome after the treatment.

Key words: leukemia, lymphoblast, hemorrhage, meningoencephalities, pial vessels

The acute lymphocytic leukaemia (ALL) is a neoplastic disease of immature lymphocytes or lymphocyte progenitor cells for either the B or T-cell lineage. At diagnosis, the leukaemia cells typically replaced normal cells in the marrow and have disseminated to various extramedullary sites, accounting for many of the clinical manifestations. The "acute" term refers to the undifferentiated, immature state of the circulating lymphocytes ("blasts") and that the disease progress rapidly with life expectancy of weeks to month if left untreated.

INCIDENCE

ALL is one of the most common malignancies diagnosed in patients younger than age 15 years, with a peak of incidence of 4-5 years of age, accounting for one fourth of all cancers and three quarters of all leukaemias in this age group. The incidence rate in adult is 1/100000 persons/year and represents 20% of adult leukaemia (1).

RISK FACTORS

ALL develops from a combination of genetic and environmental factors such as:

1. gender – male are more frequently affected
2. caucasians
3. age: over 70 years
4. previous treatment with chemotherapy or radiation therapy
5. exposure to atomic bomb radiation or to chemicals (benzene)
6. genetic disorders such as Down syndrome (in leukemia chromosomal translocations occurs regularly which may trigger oncogenes to "turn on" causing unregulated mitosis)

CLASSIFICATION OF ACUTE LEUKEMIA

There is a general classification of ALL according to the World Health Organization *(W.H.O. classification)* in:

1. B precursor leukaemia (in 75% of cases)
2. T precursor leukaemia (in 25% of cases)
3. Burkitt cell leukaemia

The morphological classification is widely used for acute myeloid leukaemia (AML) while in ALL has been supplanted by the immunophenotype. The French-American-British classification system *(F.A.B. classification)* has become generally adopted using morphology and cytochemistry supplemented by immunophenotyping. The classification does not include the biphenotypic leukemia and leukemia secondary to radio and chimiotherapy (2). In F.A.B. classification there are three types of ALL as follows:

1. L_1 – ALL with small, uniform cells with round shape, homogenous nucleus; it encounters in 75% of childhood ALL; express CD10, CD19 and in 50% of cases CD20
2. L_2 – ALL with large cells of varying size and irregular nonhomogenous nucleus; it encounters in 70% of adult ALL; express CD10, CD19 and in 50% of cases CD20

3. L_3 – ALL (L_1-Burkitt-type ALL) with large, uniform cells with round-to-oval homogenous nucleus and vacuoles (bubble-like feature) which is a very rare type of leukaemia; express CD13 or CD33 (associated with poor prognostic).

The pattern of distribution of ALL subtypes differs from adult to child. Unlike the childhood ALL, where the predominant type is ALL-L_1, in adult, the most frequent subtype is L_2 (1).

Another classification that needs to be considered is the *R.E.A.L. classification* (Revised-European-American-Classification of Lymphoid Neoplasms) which refers to all lymphoid pathology depending on the physiological degree of differentiation of B and T cells. Most of the acute lymphoblastic leukaemia in the R.E.A.L. classification is pre-B cells. These type of cells (L_1, L_2) express CD19 and in most of the cases CD20.

A classification to be considered is the European group for the immunological characterization of leukemia classification *(E.G.I.L.)* using only immunophenotyping (the groups are delineated according to the degree of cell differentiation):

1. Pro B/pre-pre B type
2. common type
3. Pre B type
4. Mature B type

NEUROLOGICAL COMPLICATIONS

Adult patients with ALL are at risk of developing CNS involvement during the course of the disease (especially patients with L_3 histology). Treatment and prognosis are influenced by this complication (3). There are fewer than 10% patients with newly diagnosed adult ALL which present CNS leukaemia (4). Signs and symptoms of central nervous system (CNS) involvement, even when it occurs, are rarely observed at the time of the initial diagnosis. These manifestations usually are: headache, nausea and vomited, lethargy, irritability, nuchal rigidity or papilledema. After the leukaemia diagnosis, tests are done in order to find out if the cancer has spread to the CNS (brain and spinal cord): lumbar puncture and CT scan. There is well known the presence of neurotoxicity as a complication of the treatment with vincristine and MTX, usually with reversibility.

1. *meningeal leukemia.* Almost one third of all leukemic patients have evidence of diffuse infiltration of the leptomeninges and cranial and spinal nerve roots at autopsy (5) with a higher incidence in childhood ALL. The CSF exam shows in most of the cases increased pressure, elevated level of proteins and low glucose level, lymphocytic pleocytosis. The flow citometry shows the presence of leukemic cells in the CSF since the CNS leukemia is primarily a pial disease (the studies of Price and Johnson) and therefore the deep perivascular spaces are infiltrated with leukemic cells. Very few cases show normal aspect of CSF. The usually used treatment is radiation therapy to the symptomatic area and intraventricular or intratechal administration of methotrexate (MTX).

2. *hemorrhages of varying sizes* represents a very common complication which can occur after the chemotherapic treatment with L-Asparaginase, by the disturbance of the balance of proteins which are important for coagulation and fibrinolysis. Another cause may be the hyperleukocytosis which occurs in ALL (6). There is a report case about a hemorrhage oculomotor paralysis, a very rare complication that occurs due to leukemic invasion in the spinal cord and oculomotor nerve during hematological remission state (7).

3. *cerebral dural sinus thrombosis* is a very rare complication in adult ALL patients (8, 9) and occurs especially after the treatment with L-asparaginase, while in children the risk is up to 37% (3). The common symptoms are dizziness, headache, diplopia and limb weakness.

4. *necrotising leukoencephalopathy* occurs most frequently especially after triple therapy: cranial radiotherapy, intratechal and intravenous MTX. Usually it appears within several days to month after the last administration of MTX or after completion of radiotherapy (10). The symptoms usually are apathy, drowsiness, and depression up to cerebellar ataxia, extrapyramidall abnormalities and akinetic mutism.

5. other manifestations which commonly occurs after the treatment are: *peripheral neuropathy, cranial nerve* involvement (usually the seventh, the third, the fourth and the sixth pairs) (11), *cerebrovascular accidents, seizures, myelopathy and neurocognitive defects.* There are reports about myelitis with neurogenic bladder secondary to chemotherapy (12).

TREATMENT

There are three stages of ALL: untreated, in remission (under 5% blasts in the bone marrow) and recurrent/refractory ALL. Because leukaemia is a systemic disease, therapy is primarily based on chemotherapy. Unfortunately the B-cell ALL does not respond well to this type of therapy and therefore it is the first form of ALL to be considered and

treated as a distinct entity on the basis of immunophenotypic and cytogenetic features by using separate protocols designed specifically for this type of leukaemia.

For the adult ALL usually there are three steps of therapy: induction therapy, consolidation therapy and the maintenance phase. The ALL 06/99 Protocol recommends a two phase's induction therapy using Dexamethasone, Vincristine and Adriblastin for faze 1 and respectively Dexamethasone, Cyclophosphamide, Cytosar or Purinethol for faze 2. As consolidation, therapy with L-asparaginase and Dexamethasone is used. The treatment of CNS, also known as CNS sanctuary therapy or CNS prophylaxis, is usually given during each phase of therapy consisting in intensive intratechal or systemic administration of chemotherapic agents (ARA-C 40 mg, MTX 15 mg, Dexa 4 mg) with CNS relapse rate under 2% in some studies. The cranial irradiation (24 Gray/12 administrations) prevents CNS relapse BUT has the risk of neurotoxicity and brain tumors.

There are mentioned some modern therapies such as: stem cell transplantation, bone marrow transplant, biologic (immune) therapy and tyrosine-kinase inhibitor therapy.

PROGNOSTIC

The prognosis in adults with ALL can be predicted from clinical and laboratory findings, especially the patient's age. Remission duration is an important determinant of long term survival.

Prognostic Factors Indicating Short Remission Duration:

1. high WBC count at presentation (13):
   - critical value for worse prognosis currently is 25,000-35,000 per μL
   - counts > 100,000 per μL are associated with poor prognosis
2. age: less than 1 year and over 10 years – worse prognosis in childhood (13), over 50 years of age – worse prognosis in adult (14)
3. late achievement of complete remission (more than 4-5 weeks of therapy) (14, 15, 16)
4. cell markers
   - possibly ALL with myeloid antigens (mixed lineage or hybrid)
   - possibly pre-T-ALL

   B-cell ALL is poor prognosis (13)
5. chromosomal abnormalities with poor prognosis: t(4;11), Ph-ALL: t(9;22), t(8;14), t(1;19). The last translocation is found in 5% cases of childhood ALL and in 25% cases of adult ALL (17)

Additional factors reportedly affecting prognosis:

1. organ involvement at presentation (extensive lymphadenopathy, hepatomegaly, splenomeglay, CNS involvement, mediastinal involvement)
2. male gender (13)
3. elevated LDH (14, 15, 16)
4. elevated GGT levels (14, 15, 16)
5. low platelet count (14, 15, 16)
6. degree of bone marrow involvement
7. number of immature forms in the peripheral blood
8. weight loss
9. race
10. hyperleukocytosis (over 50000/ml) – is a bad prognostic factor (18)
11. β_2 microglobuline is associated with a poor prognosis in adults (lower response rate, increased in incidence of CNS involvement, worse survival) (19)
12. patients with molecular evidence of bcr-abl fusion gene (especially cases with B-cell lineage disease)

There are follow-up studies covering a period of 5 years about the incidence and frequency of CNS relapses in long term surviving adults, age eighteen and over. CNS relapses, a major determinant for CNS prophylactic and maintenance therapy, were observed in 75% of the patients with ALL (20). A randomized study of prophylactic CNS treatment for adults with ALL demonstrated a significant prolongation of CSF relapse-free interval but did not improve hematologic remission or survival (21).

After conventional chemotherapy, the complete remission rate in adult ALL is about 79%, but the survival rate is 32% for the next three years and after five years is about 24% (22). Long term follow up of 30 patients with ALL in remission for at least 10 years has shown 10 cases of secondary malignancies (23).

CASE PRESENTATION

It is presented the case of a 44 years old female patient, with a personal history of B-virus hepatitis and uterine fibromyoma, diagnosed in May 2006 with pro-B acute lymphoblastic leukemia, CALLA+ (common acute lymphoblastic leukemia antigen) with hyperleucocytosis (F.A.B. and E.G.I.L. diagnostic criteria) and CD10, CD19, CD34 positive on flow cytometry. She was treated according to the ALL 06/99 Protocol, comprising induction, consolidation and CNS prophylaxis with cytosine

arabinosid (40mg), MTX (15mg) and dexamethasone (4mg). The bone marrow biopsy performed after induction revealed a good early outcome.

During the course of the disease she presented multiple complications:

1. primary fibrinolysis syndrome (with a very low fibrinogen, up to 70mg/dl and normal coagulation studies) manifested by menorrhagia and intermenstrual bleeding resistant to medical treatment, for which uterine artery embolization was needed.
2. marked depression and confusional state. Although she did not have a personal history of psychiatric problems, she presented the above mentioned symptoms probably due to a combination of her main condition, hospitalization and steroid therapy.
3. approximately three months after the onset, she presented severe fatigue, intense cervical spine pain and decreased muscle strength in the right limbs, for which she was readmitted.

On admission in the Neurology Department the patient was anxious, pale, with impalpable spleen and cervical, axillary and inguinal lymph nodes, with a hardened liver whose lower margin was 3 cm below the costal rim. The blood pressure was 110/60 mmHg and the pulse 72 beats/min. The neurological exam revealed marked neck stiffness, discreet facial asymmetry, right hemiparesis, and tendon reflexes diminished on the right, Babinski's sign present bilaterally.

Blood test results showed 3000/ml leucocytes, normochromic macrocytic anemia (hemoglobin = 7.1 g/dl, MCV = 106 fl, MCH = 31.1 pg), 269000/ml platelets.

The lumbar puncture revealed a bloody CSF, Pandy's test +++, proteins = 49 mg/dl, frequent red blood cells and 10/ml white blood cells, highly suggestive of subarachnoid hemorrhage.

The head CT scan was unremarkable and the angiographic exam as well.

The head MRI showed:

1. small diffuse cerebral hemispheric white matter hyperintensities (left > right) on FLAIR and T2 weighted images with cortico-subcortical fronto-parietal distribution, with patchy aspect that descend assimetrically in the centrum semiovale white matter; without gadolinium enhancement
2. focal thickening of the meningeum near falx cerebri and on the left fronto-parietal convexity, with gadolinium enhancement on site. MR aspect suggests neoplazic meningoenkefalitis
3. linear periventricular hyperintensities on FLAIR and T2 weighted images without gadolinium enhancement, suggesting vasculodegenerative lesions

The final diagnoses were subarachnoid hemorrhage and leukemic meningoencephalitis.

Our patient treatment comprised in systemic antiedematous drugs (mannitol), cerebral vasodilator (nimodipine) and steroids (dexamethasone) and intrathecal or systemic chemotherapy (MTX or ARA-C) twice a week followed by radiotherapy (24 Gray/ 12 administrations). Four months later a bone marrow biopsy revealed a hypercellular marrow showing hematological remission. The control lumbar puncture revealed an almost normal aspect of CSF with Pandy test +, few blood cells (35/mm^3), proteins = 55 mg/dl, glucose = 76mg/dl.

COMMENTS

There are several peculiarities regarding the presented case. First of all the age of the debut is usually, as shown, lower than 15 years of age, while in adult ALL represents 20% of adult leukemia. The evolution of the simptomatology of this patient is uncommon, with primarily fibrinolysis and the very precocious involvement of the CNS (the first three month after diagnoses of the hematological disease).

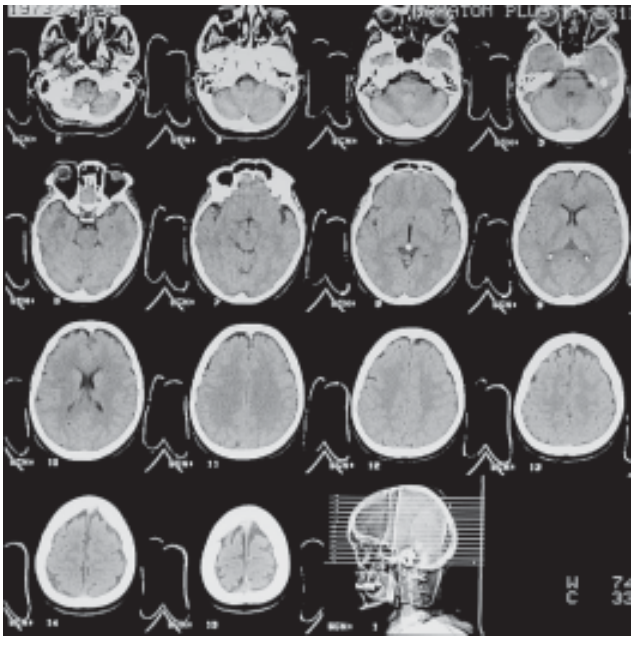

Figure 1
Normal aspect of the cerebral CT scan

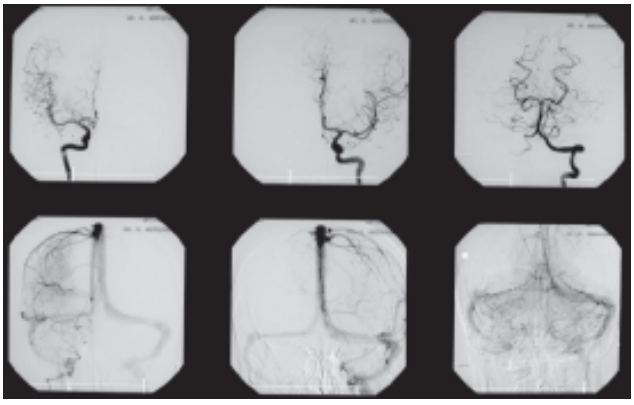

Figure 2
Normal aspect of the cerebral angiography

The two neurological manifestations were subarachnoid hemorrhage and leukemic meningoencephalitis. As we mentioned previously the possible explanation could be the involvement of the walls of pial vessels, the extension of the leukemic infiltrate to the deep perivascular spaces (CSF with leukemic cells) as well as the diffuse inflammation of the vessel wall with its consequence – the rupture of the vessel wall.

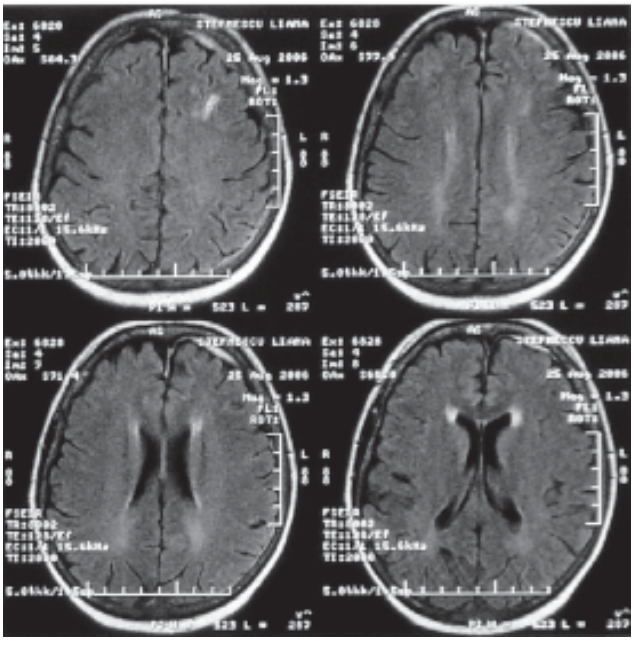

Figure 3
Cerebral MRI – FLAIR image – white matter hyperintensities cortico-subcortical fronto-parietal, without gadolinium enhancement; focal thickening of the meningeum near falx cerebri and on the left fronto-parietal convexity, with gadolinium enhancement on site

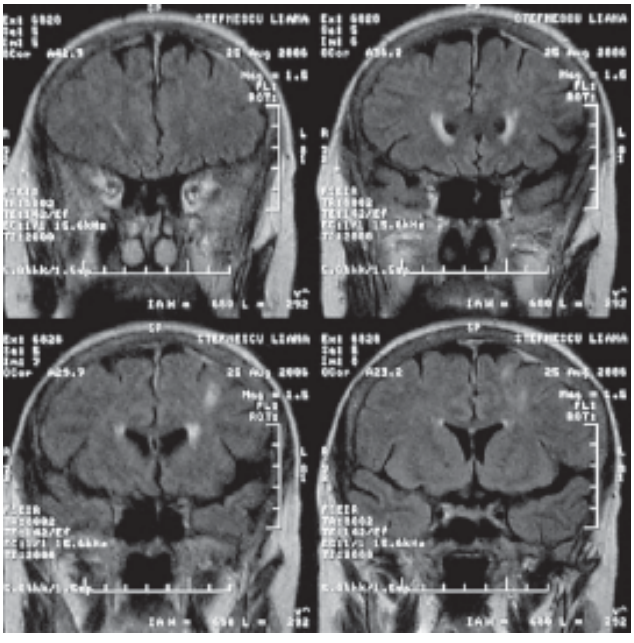

Figure 4

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