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Case Report

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Cryptococcal neuroinfection in an adult patient with chronic B-lymphatic leukaemia with medium risk – a case report

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Ladislav Slovacek[1,2,3], Ladislav Jebavy[1,2]

[1] Department of Field Internal Medicine, University of Defence, Faculty of Military Health Sciences, Hradec Kralove, Czech Republic
[2] 2nd Department of Medicine, Charles University Hospital and Medical Faculty, Hradec Kralove, Czech Republic
[3] Department of Clinical Oncology and Radiotherapy, Charles University Hospital and Medical Faculty, Hradec Kralove, Czech Republic

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Summary

Background Chronic B-lymphatic leukaemia is one reason for the development of secondary immunodeficiency due to a decrease of antibody immune activity (hypogammaglobulinaemia) and a decrease of T-cell immunity. Cryptococcosis is an infectious disease induced by Cryptococcus neoformans fungus. A high incidence was revealed in immunocompromised patients, above all in patients with AIDS or with haematological malignancies usually with a primary focus in the lungs and with characteristic spread into the cerebral dura mater and rarely into the kidneys, prostate, liver, bones and skin.

Aim The aim of the study was to report a case of fatal Cryptococcus neoformans meningitis in an adult patient with chronic B-lymphatic leukaemia.

Material/Methods It is a case study report of a 74-year-old man who presented with a four-year history of B-CLL admitted to the Department of Clinical Haematology with suspected neuroinfection. Symptoms included headache and sleepiness. Diagnostic work-up comprised neurological investigation, magnetic resonance imaging of the brain, lumbal puncture with microscopic, cytological and biochemical investigations of cerebrospinal fluid and investigations of blood serum for borellia, toxoplasma, Cytomegalovirus and Epstein-Barrs virus. Cultural investigation of the fluid verified two colonies of the fungus Cryptococcus neoformans. Despite intravenous and intrathecal administration of antibiotics and steroids the patient died due to septic shock.

Conclusions Prognosis of cryptococcosis is very serious especially in immunocompromised patients and in the case of disseminated form is always infaust.

Key words **cryptococcosis • chronic B-lymphatic leukaemia • meningitis**

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Author's address: Ladislav Slovacek, University of Defence, Faculty of Military Health Sciences, Department of Field Internal Medicine, 1575 Trebesska Str., 500 01 Hradec Kralove 1, Czech Republic, e-mail: ladislav.slovacek@seznam.cz

Background

Chronic B-lymphatic leukaemia (B-CLL) is a slightly aggressive (malignant) lymphoproliferative disease originating on the basis of proliferation of clonal, malignant transformed mature B-lymphocytes [1,2]. This type of leukaemia is the most frequent leukaemia of adults in Europe and North America, where it comprises 25–30% of all leukaemias. Its incidence in Europe is 3/100000; it occurs 2 times more frequently in men than women and usually in persons over the age of 50 [3,4]. Probably lymphotropic viruses witch inhibace apoptosis in an invaded B cell and the gene bcl-2 participate in aetiopathogenesis of B-CLL [5]. The result of its increased expression is the inhibition of apoptotic death of pathologic lymphocytes. The clinical picture of B-CLL is expressed with a long (at least ten years) asymptomatic period. The only symptom of the disease in this period is lymphocytosis in the peripheral blood and bone marrow. Clinical stages of B-CLL are classified by NCI-WG (National Cancer Institute – White Granulocytes) (it is a modification of the classification by Raie and Binet) [1,2]: 1. B-CLL with low risk (lymphocytosis in peripheral blood), 2. B-CLL with medium risk (lymphocytosis in peripheral blood and lymphadenopathies or splenomegaly/hepatomegaly), 3. B-CLL with high risk (lymphocytosis in peripheral blood with anaemia (haemoglobin <110g/litre) or with thrombocytopenia (number of thrombocytes $<100\times10^9$/litre). The diagnosis of B-CLL is based on NCI-WG criteria [5]: 1. lymphocytosis in peripheral blood (absolute number of lymphocytes is 5000/ml), 2. lymphocytes are small and mature with imunophenotype B1 (CD5+ B cells). The strategy of B-CLL therapy arises from the fact that treated in a traditional way it is an incurable disease. The therapy of B-CLL is indicated mainly at advanced stages of the disease and consists of systemic palliative chemotherapy [1–3]. Its aim is induction of apoptosis in B-CLL cells. Applied cytostatics include alkylac substances (chlorambucil) in monotherapy or in combination with corticosteroids for simultaneous thrombocytopenia and autoimmune haemolytic anaemia. In recent years, purine analogues (fludarabine monophosphate, 2-chlordeoxyadenozine) have been administered [5]. Haematopoietic stem cell transplantation and immunotherapy with monoclonal antibodies (anti-CD20 and anti-CD40) are also applied. The median survival time in patients with B-CLL, diagnosed at the initial phase, is 8–10 years [1,2]. Of essential importance in prognosis of B-CLL is the determination of chromosomal aberrations (deletion 11q23, trisomia 12) by means of FISH method (fluorescence *in situ* hybridization). A mutation of gene p53 is also associated with poor prognosis [1].

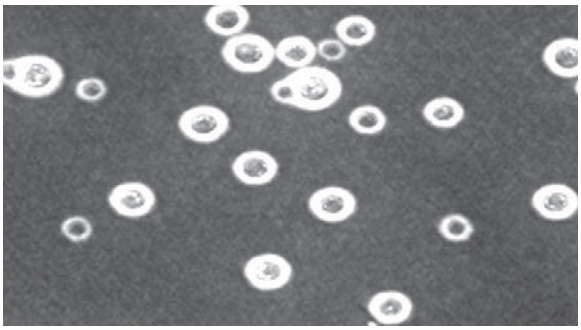
Aim

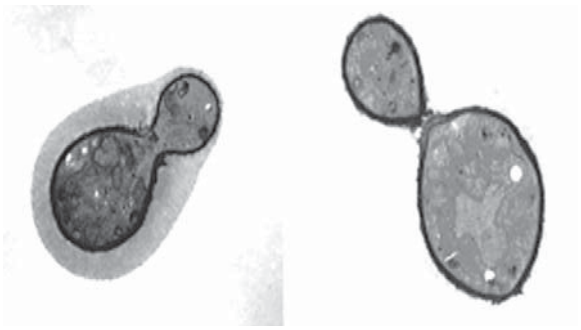
B-CLL is one reason for the development of secondary immunodeficiency due to the decrease of antibody immune activity (hypogammaglobulinaemia) and the decrease of T-cell immunity. Immune system disorders include frequent infections, usually opportunistic and recidives of respiratory infections (bacterial, viral, fungal, etc.) [3].

Case Report

A 74-year-old man who presented with a four-year history of B-CLL with medium risk treated by cyclophosphamide in the dosage of 50mg daily together with prednison administered in the dose of 10mg daily was admitted to the Department of Clinical Haematology for further clinical, laboratory and auxiliary investigations and therapeutic intervention for suspected neuroinfection on November 20, 2004. The patient had headache, was sleepy and was meningeal.

First, magnetic resonance imaging of the brain was carried out verifying diffuse brain atrophy with leukoaraiosis picture. The picture does not verify progressive multifocal leukoencephalopathy. On November 20, 2004, the patient underwent a neurological investigation with the





Figures 1–2. Cryptococcus neoformans fungus in electronic microscope with characterized mucopolysaccharide capsule.

conclusion: 1. progradual apatico-abulic syndrome, prefrontal syndrome, upper meningeal syndrome, suspected tumorous infiltration mening according to fluid, magnetic resonance not verified, 2. febrile status of unclear aetiology, unlikely central cause. We performed lumbal puncture. Microscopic, cytological and biochemical investigations of the cerebrospinal fluid were negative. Cultural investigation of fluid verified >10 colonies of the fungus Cryptococcus neoformans. Also we performed investigations of blood serum for borellia, toxoplasma, Cytomegalovirus and Epstein-Barr virus. All investigations were negative. In the patient therapy was applied with intravenous amphotericin B in the dose of 50mg a day and intravenous empirically wide-spectrum antibiotic (Tazocine in the dose of 4.5 grams 3× a day). Dexamethasone in the dose of 4mg and amphotericin B in the dose of 0.05mg were applied intrathecally 1× a week. Before intrathecal application of dexamethasone and amphotericin B we performed subscription of fluid to microscopic, cytological, biochemical and cultural investigations. On December 1, 2004, we performed another control lumbal puncture during intensive antimycotic therapy. Microscopic, cytological and biochemical investigations of the cerebrospinal fluid were negative. Cultural investigation of the fluid verified two colonies of the fungus Cryptococcus neoformans (regression of number of colonies) (Figures 1 and 2).

The patient's therapy was retained without change. On December 17, 2004, the patient was meningeal and he was febrile. We performed further control lumbal puncture. Microscopic, cytological and biochemical investigations of fluid were negative. Cultural investigation of fluid verified >10 colonies of the fungus Cryptococcus neoformans (progression of number of colonies). For febrile status we completed cultural investigations of the nose, neck, sputum, rectum, urine and haemoculture. For progression of B-CLL, cyclophosphamide was added to the system therapy in the dose of 100mg a day.

On December 20, 2004, due to the character of the disease – progradual cryptococcal neuroinfection in the immunocompromised patient through intensive casual therapy – it was necessary to apply symptomatic therapy only. On December 21, 2004 at 15:40, the patient died due to septic shock (urosepsis with progradual cryptococcal neuroinfection) – autopsy proved cryptococcal meningitis.

Discussion

Cryptococcosis (synonym: torulosis, European blastomycosis) is characterized as an infectious disease induced by Cryptococcus neoformans fungus usually with a primary focus in the lungs and with characteristic spread into the cerebral dura mater and rarely into the kidneys, prostate, liver, bones and skin. The disease occurs sporadically; 2 times more frequent incidence is proved in men at the age of 40–60 compared to women [4]. Frequent incidence was revealed in immunocompromised patients, above all in patients with AIDS or with haematological malignancies. The agent is spread in man's environment mainly in soil substrates containing droppings of some birds (pigeons). The fungus's hosts are man, cats, dogs, horses and primates. An infectious dose is significant for its low pathogenicity level in healthy adults. Route of transmission is especially through inhalation. The incubation period is not well known; in lung diseases and central nervous system disorders months or even years are indicated. Brain damage includes above all diffuse meningitis, meningela granulomes, brain infarctions and malatic focuses. The most frequent symptom in meningitis is cefalea with meningism manifestation. The patient usually makes an appointment with a physician for cefalea, visual disorders, psychological disorders – anxiety, depression, memory

loss, concentration problems, psychomotor anxiety, dysartria, etc. [4]. Diagnosis of cryptococcosis is based on microscopic evidence of budding fungi surrounded by a light capsula in a preparation made from sputum, purulent exudate or cerebrospinal fluid. A specific antigen may be detected in blood, urine or liquor with latex aglutination. The diagnosis of cryptococcosis is significantly proved by cultivation and identification of the infective agent.

The therapy of cryptococcal meningitis is based on systemic antimycotic therapy [4]. A combination of amphotericin B with 5-flucytosin may be the drug of choice: amphotericin in the dose of 0.3mg/kg/day intravenously for a period of 6 weeks, 5-flucytosin in the dose of 150mg/kg/day per os in 4 partial doses for a period of 6 weeks [4]. This therapy is successful approximately in 85% of patients without AIDS. In patients with AIDS, this therapy is successful only in 50%. Cured patients need a long-term and likely a whole-life suppressive therapy best of all with fluconazol in the dose of 200mg daily per os. Unfavourable effects of the above-mentioned antimycotic therapy are dyspeptic complaints, skin manifestations (unspecified dermatosis, anaemia, leukopenia and thrombocytopenia), elevation of liver transmitases and nitrogenous catabolites. Prognosis of cryptococcosis is very serious especially in immunocompromised patients and in the case of disseminated form is always infaust.

Conclusions

In the present report we describe cryptococcosis of an immunocompromised patient as a rare and especially the incidence of cryptococcal meningitis in an adult patient with chronic B-lymphatic leukaemia with medium risk.

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