Signature: © Pol J Radiol, 2012; 77(1): 54-57

Polish Journal of Radiology
www.PolRadiol.com

CASE REPORT

Received: 2011.12.20
Accepted: 2012.01.19

Invasive fungal infection of the central nervous system in a patient with acute myeloid leukaemia

Anna Janik-Moszant[1], Aleksander Matyl[1], Iwona Rurańska[1], Agnieszka Machowska-Majchrzak[2], Ewa Kluczewska[3], Tomasz Szczepański[1]

[1] Department of Pediatric Hematology and Oncology, Medical University of Silesia, Zabrze, Poland
[2] Department of Neurology, Medical University of Silesia, Zabrze, Poland
[3] Department of Radiology and Radiodiagnostics, Medical University of Silesia, Zabrze, Poland

Author's address: Ewa Kluczewska, Department of Radiology and Radiodiagnostics, Medical University of Silesia, Zabrze, Poland, e-mail: ewakluczewska@eranet.pl

Summary

Background: Although the new intensive chemotherapeutic programs introduced recently into hemato-oncological therapies have led to a higher number of recoveries, persistent neutropenia favours the spread of severe infections, frequently fungal infections. Systemic fungal infections in patients treated for proliferative diseases of the hematopoietic system are characterised by a severe, progressing course and high morbidity.

Case Reports: We present a case report that demonstrates the diagnostic problem of lesions in the central nervous system which developed following the fourth block of chemotherapy in an eight-year-old boy treated for acute myeloid leukaemia. The risk factors, high values of the inflammatory parameters and imaging results enabled us to diagnose a fungal infection of the central nervous system.

Results: A fast improvement in the clinical condition of the patient after the applied antifungal therapy and the regression of lesions in the central nervous system shown in the imaging studies confirmed our final diagnosis.

Key words: children • myeloid leukaemia • fungal infections

PDF file: http://www.polradiol.com/fulltxt.php?ICID=882582

Background

The last two decades have witnessed a dramatic increase in fungal infections in hemato-oncological patients [1]. Although the new intensive chemotherapeutic programs introduced recently into treatments have led to a higher number of recoveries, persistent neutropenia favours the spread of severe infections, frequently fungal infections [2].

The majority of fungal infections are opportunistic infections caused by commensal strains of the skin and mucosa or by saprophytic strains of the external environment. Among the most commonly diagnosed pathogenic factors are funga *Candida* and *Aspergillus*, less frequently – *Fusarium* and *Mucorales* [3].

In the beginning, the clinical picture of an invasive fungal infection is hardly specific and dependent on the organ attacked. A common symptom, and usually the first one to occur, is fever that persists despite an applied antibiotic therapy [4].

On account of high mortality (approx. 50–90%) related to systemic fungal infections in hemato-oncological patients, the risk groups and risk factors of fungal infection have been singled out, which should enable early treatment.

Even modern diagnostic and laboratory technologies, including microscopic tests, microbiological methods, serologic tests and molecular biology methods make it possible to confirm – in accordance with EORTC/MSG criteria – the fungal etiology in as few as 20–30% of cases during the life of a patient [5]. This is often due to a difficulty in obtaining the test material and a necessity to expose a patient to additional invasive procedures. Usually the diagnosis is

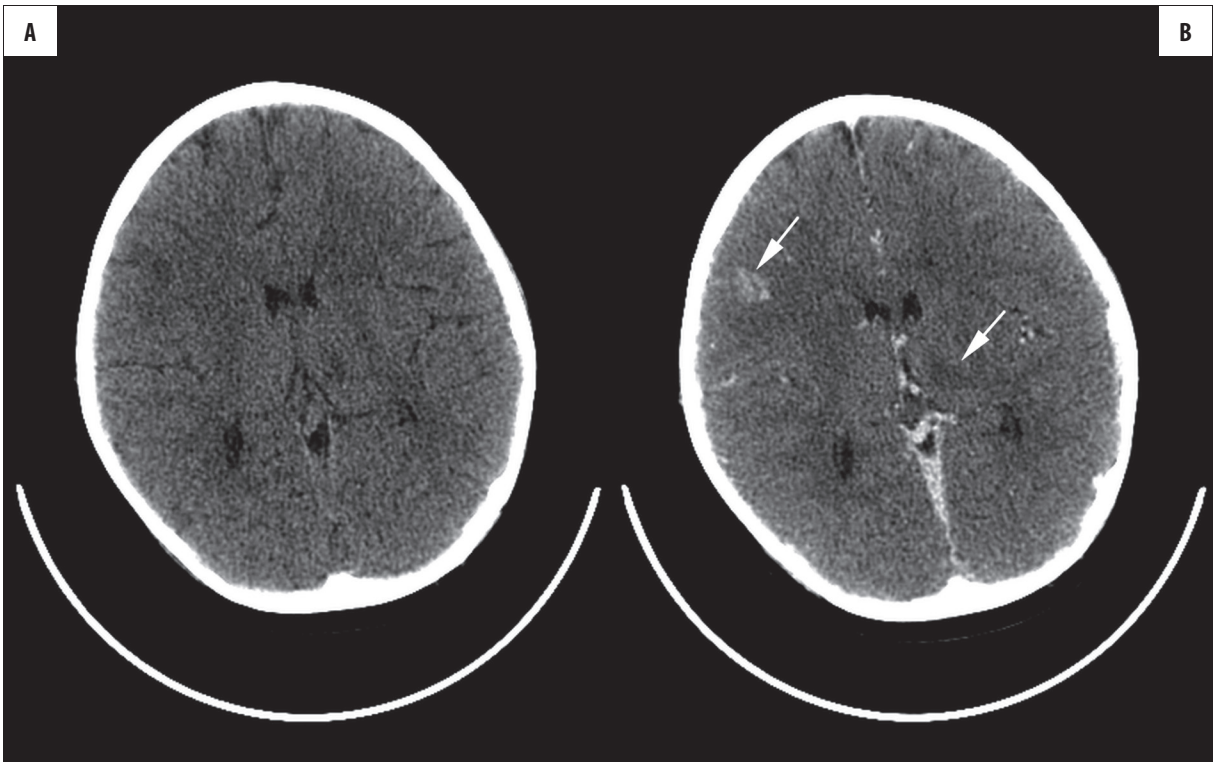

Figure 1. (**A**) non-contrast CT scan at the level of thalamus showing hypodense foci in the left thalamus and hypodense lesion in the right frontal lobe. (**B**) after infusion of iodinated contrast agent, a heterogeneous enhancement of the lesion.

made on the grounds of a combined interpretation of risk factors, clinical symptoms and imaging results.

Treating fungal infections is long and difficult, and it requires a comprehensive knowledge of pharmacokinetics in adjusting medication. Still, it often runs the risk of side effects [2].

Case Reports

An eight-year-old boy was referred to the Clinic with a suspicion of a proliferative disease of the hematopoietic system. For a few days prior to the admission to the Clinic, the boy suffered from subfebrile temperature and headaches. At admission, his general condition was good; a physical examination revealed splenomegaly. After additional tests and examinations, the boy was diagnosed with acute myeloid leukaemia (type M5 acc. to FAB) and subjected to treatment with the AML BFM Interim 2004 program for a high-risk group [6]. His chemotherapy was complicated by the occurrence of bone marrow aplasia with accompanying neutropenic fever, stomatitis, posthitis, otitis media, persistent abdominalgia and diarrhoea.

On the fifth day following the completion of the fourth chemotherapy block – consolidation protocol (haM) – the patient's temperature rose to 39°C. Three days later he started complaining of a severe headache and diplopia. Moreover, behaviour disturbances appeared in the form of excitation alternating with apathy, as well as confusion.

A neurological examination revealed asymmetry of the pupils (L>R), a left-sided paresis with positive pathological reflexes in the upper and lower limb, increasing meningeal signs and gradual deterioration of the patient's condition, which led to a coma.

The laboratory tests showed: thrombocytopenia (19×10^9/l), leucopenia (0.1×10^9/l), elevated inflammatory parameters (CRP – 387.55 mg/l), and pleocytosis of 12/3 in the cerebrospinal fluid, as well as a slightly increased protein concentration, i.e. of 618 mg/l.

Both blood and urine culture were aseptic, and no fungi in blood serum or cerebrospinal fluid were found in the tests for Aspergillus and Candida antigens. Myelogram and lumbar puncture excluded the relapse of the disease. A CT scan showed three hypodense foci of 6–10 mm in diameter within the left thalamus and lesions in the right frontal lobe (Figure 1). Because the radiological image was ambiguous, the diagnostics was extended by an MRI which showed some scattered lesions of various sizes and abnormally high signal, which might have indicated inflammatory lesions of fungal aetiology (Figure 2). The findings of abdominal USG, chest CT and ophthalmological examination were normal.

On the grounds of the neuroimaging examination, the clinical condition of the patient and additional tests and studies a potential fungal infection of the central nervous system was diagnosed.

Fluconazole, included in the treatment as a preventive measure, was replaced with voriconazole administered in a dose of 2×200 mg. On the seventh day, a slow improvement of the general condition of the child was observed with regression of neurological symptoms. The patient was administered the medication for 8 weeks intravenously and

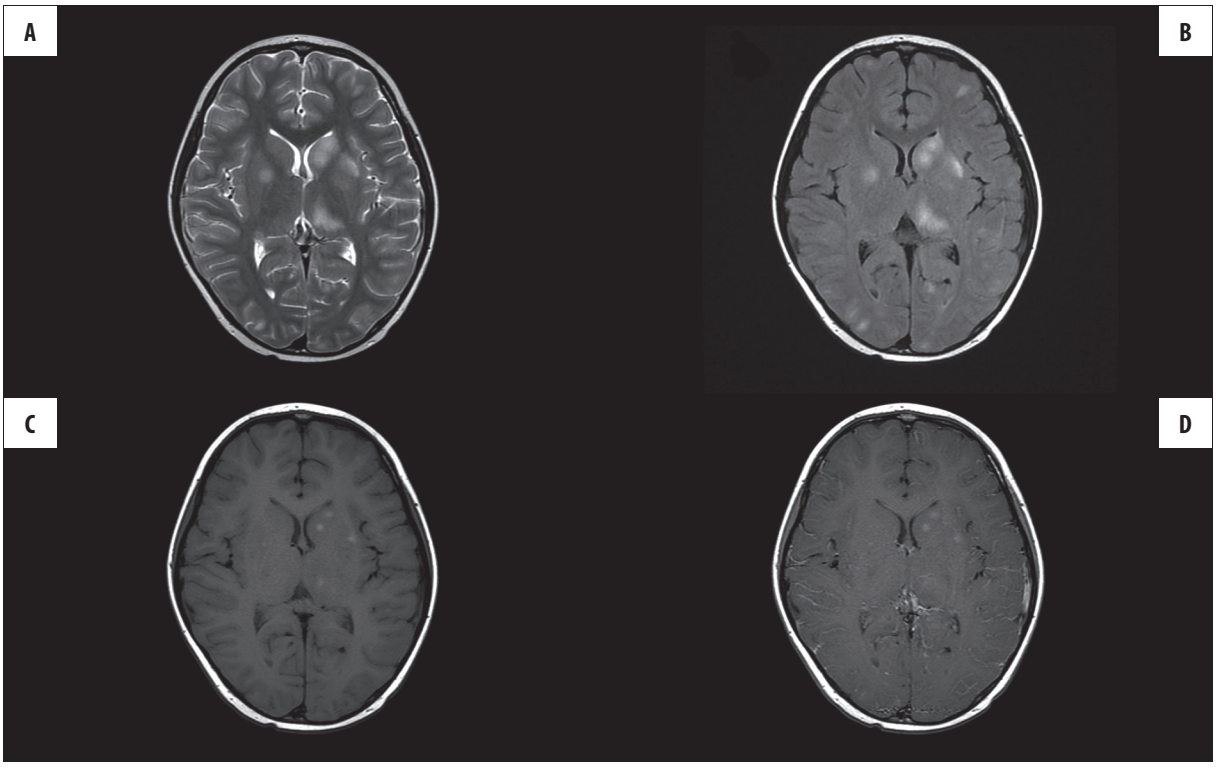

Figure 2. MRI of the brain. (**A**) Coronal SE T2-weighted image showing multiple lesions with high signal intensity, much better visible in FLAIR sequence (**B**). (**C,D**) Numerous scattered inflammatory lesions enhancing uniformly in different brain structures.

then orally until the 12th week. At the same time, the boy was given broad-spectrum antibiotics.

Brain imaging studies that followed confirmed a gradual recession of the lesions. The follow-up brain MRI performed after completing the treatment for leukemia showed only minor post-inflammatory lesions, asymptomatic in neurological examination.

Discussion

Systemic fungal infections occurring in patients treated for proliferative diseases of the hematopoietic system are characterised by a severe, progressing course and high morbidity, reaching up to 90% in case of aspergillosa [5,7,8].

Fungal infection of the central nervous system is diagnosed in 7% of children treated for acute leukaemia. The most frequent etiological factor is *Aspergillus*, the second – *Candida* [8].

The major factor responsible for the development of fungal infection in children suffering from acute leukemia is post-chemotherapy neutropenia. Deep neutropenia, of $<0.2\times10^9$/l, which often persists for more than two weeks, is observed in patients treated for acute myeloid leukaemia. These children as well as children after transplantation are considered the group at the highest risk of an invasive fungal infection [2].

We diagnosed acute myeloid leukaemia in our patient. One of the first symptoms of a progressing fungal infection is often a persistent fever not responding to the antibiotics applied in patients undergoing immunosuppressive treatment [4]. Another characteristic is a fast development of other inflammatory symptoms: increased level of C-reactive protein and procalcitonin, as observed in our patient.

Diagnostics aimed at identifying the etiological factor is very difficult, with only 25% of identified fungal infections in living patients. The most reliable diagnostic tests are the measurements of soluble antigens from the fungal cell wall: galactomannan, mannose and (1,3)-β-D-glucan, which should be performed in neutropenic patients from high-risk groups, twice a week. Their sensitivity is estimated at 67–100% [8–11]. Among the latest methods used in the diagnostics of fungal infections there is a polymerase chain reaction. The test is characterised by high sensitivity and specificity, thus enabling the identification of the genetic material of the fungus [12].

Since reliable laboratory tests which could explicitly confirm a fungal infection are not widely available, the diagnosis should be supplemented with imaging studies, and the obtained findings should be analysed comprehensively along with the evaluation of the overall condition of the patient. Neuroimaging studies (contrary to high-resolution CT scan of the lungs and abdominal ultrasound) are not commonly performed in the diagnostics of fungal infections. However, they are necessary in suspicion of a fungal infection developing in the central nervous system [1,13,14] when they are fundamental for the diagnosis of fungal infection. On MRI, lesions tend to be slightly hypointense on T1 sequences and iso- to slightly hyperintense on T2 sequences. All lesions show a different (diffused and prominent) enhancement on CT and MRI after infusion of i.v. contrast. There are no characteristic locations within the

brain [15]. In the case of our patient, the magnetic resonance imaging of the brain turned out to be of particular importance, as presented in the case study.

Quick diagnostics enables an early diagnosis and prompt introduction of treatment, reducing the incidence of organ fungal infection and hence the mortality rate [2].

Antimycotic prevention, both primary and secondary, is directed at patients undergoing immunosuppressive treatment, with the most commonly prescribed medications being triazoles, including fluconazole [2,16].

Persistent fever and ineffective broad-spectrum antibiotic therapy should be an indication to include empirical treatment with antimycotic medicines [16]. At the same time, it is crucial to continue diagnostic tests, which aim at establishing the true cause of the neutropenic fever. The medicine of choice recommended in empirical treatment is a liposomal form of amphotericin B, or alternatively – caspofungin [2,17]. On the grounds of imaging results, positive test results for fungal infection, as well as possible coexisting clinical symptoms, a decision should be made to include a preemptive therapy. The choice of medicine will depend on such factors as: type of identified pathogen, location of lesions and their advancement, immunosuppressive condition of the patient, coexisting diseases and organ dysfunctions, and should take into account the level of toxicity of the prescribed medicine. In the case of an invasive fungal infection, the drug of choice is echinocandin or one of the forms amphotericin B; in the systemic treatment of aspergillosa – voriconazole, and when contraindicated – a liposomal form of amphotericin B [18,17].

When refractoriness to first-line therapy appears, a combined therapy should be taken into consideration, such as combination of caspofungin with voriconazole or a liposomal amphotericin B, and recently – posaconazole [19].

In the case of our patient, the suspicion of a fungal infection was raised on the third day of fever, and the choice of medicine was dependent on the location of the organ lesions. Voriconazole is a medicine which penetrates well to every tissue, obtaining a particularly high concentration in the cerebrospinal fluid. It is recommended as a first-choice drug in fungal infections of the central nervous system [2,7,12]. It is characterised by a broad anti-fungal activity, fungistatic effects, and fungicidal properties against Aspergillus. According to directives, the combined treatment time of a substantiated fungal infection of the central nervous system leading to regression of all symptoms of infection should be at least 12 weeks. Voriconazole is a well-tolerated medicine, and among its most common side effects, observed also in our patient, there are visual disturbances, hypertransaminasemia and allergic skin reactions [14,20].

The above presented case study demonstrates the diagnostic problem of lesions in the central nervous system which developed following the fourth block of chemotherapy in a boy treated for acute myeloid leukaemia. In the initial differential diagnosis we considered also bleeding to the central nervous system as well a relapse of the basic disease – both excluded in routine additional examinations. The risk factors, high values of the inflammatory parameters and imaging results enabled us to diagnose a fungal infection of the central nervous system. A fast improvement in the clinical condition of the patient after the applied antifungal therapy and the regression of lesions in the central nervous system shown in the imaging studies confirmed our final diagnosis.

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