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The radiologic diagnosis of invasive fungal infections in neutropenic children

Fungal infections have substantially increased in incidence over the past two decades, both in adults and children (1, 2). The high risk group of fungal infections includes patients with childhood cancers and profound neutropenia, who have received high doses of chemotherapy (with or without stem cell rescue), but also including those who have received solid organ transplants, and those with immunosuppressive diseases such as AIDS (5). About 20–30% of children with fungal infections is treated due to leukemia, 10–15% due to lymphoma and 5% due to solid tumours (9). Patients with invasive fungal infection whose hematological neoplasm was not in remission had a sixfold or greater mortality rate than the ones in remission (3, 6).

In immunocompromised individuals fungal infections develop as systemic infection. Even though yeast such as *Candida albicans* may cause these infections, molds are more frequently detected, with *Aspergillus flavus* and *Aspergillus fumigatus* being most widely isolated. Invasive fungal infection caused by other species, such as *Pseudallescheria boydii*, *Rhisopsus arrhizus*, *Fuscarium* species and *Alternaria* species has also been observed, especially in immunocompromised patients (5, 6, 8,10). In the past, patients did not survive these infections: they died of either the infection or their underlying disease because of delays in chemotherapy. Newer approaches, including new antifungal agents and growth factors, are being used in these patients.

The diagnosis of fungal infections is based on clinical observations, radiological and laboratory methods, and molecular biological techniques. Laboratory methods depend for the most part on isolation of the fungus in culture, on its detection in clinical material by direct microscopic examination and on the detection of an immunological response to the pathogen or some other marker of its presence, such as a metabolic product (8, 9). The diagnosis based on laboratory methods and molecular biological techniques is the most certain, but it is difficult to perform, time-consuming and expensive. The acute, culminant form of infection can progress rapidly from hours to days and can lead to death. Therefore, early diagnosis is important and increases overall response rates.

The aim of the study was the analysis of the early clinical picture and radiologic findings of patients with systemic fungal infections.

MATERIAL AND METHODS

The subjects of this study were patients with fungal systemic infections who were treated due to childhood cancers in the Department of Hematology and Oncology Medical University of Lublin in the years 2001–2002. The early symptoms of fungal infection and the radiologic findings were analyzed.

RESULTS

The deep systemic fungal infections were recognized in eight children, five patients were male and three patients were female. The median age of the patients was seven years (range 1–17 years). Patients were treated due to acute lymphoblastc leukemia (ALL) – four patients, acute myelogenous leukemia (AML) – two patients and non-Hodgkin lymphoma (NHL) – two patients. In all the patients manifestations of fungal infection were observed during severe bone marrow suppression secondary to chemotherapy treatment of neoplasm.

All the children presented with fever (above 39°C). In two patients neurological disorders, such as headache and dizziness and in seven patients cough and dyspnoea were observed. The intravenous antibiotics were applied without response. The children's condition was worse. Isolation of the fungus or bacterial cultures in clinical material (specimens of skin, mucous membranes, blood, urine, cerebrospinal fluid) was negative.

In seven patients who presented clinical symptoms of respiratory tract the X-ray examination was normal. However, the radiological pulmonary changes, probably because of fungal infection, were founded in computed tomographic scans (CT) in all of them. The most common CT finding were pulmonary nodules, either solitary in five of seven patients (Fig. 1) or multiple in two patients (Fig. 2). In one patient with cerebral manifestation of the infection, MRI of the central nervous structures showed marked abnormalities of the brain (Fig. 3).

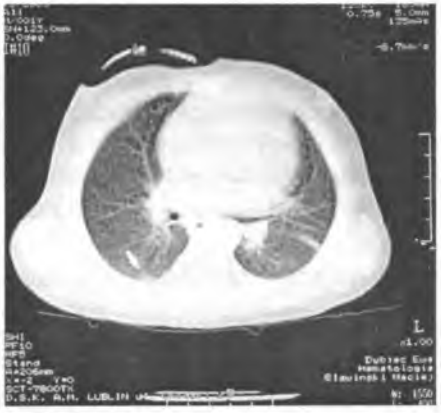

Fig. 1. Image from a male aged 1 year. Solitary nodule, probably caused by fungal infection on computed tomography scan

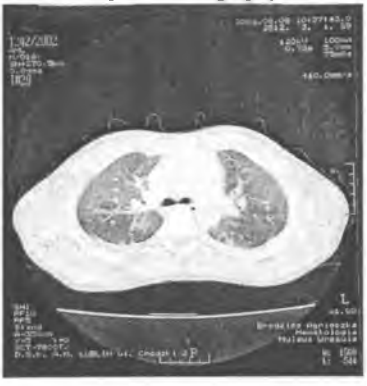

Fig. 2. Image from a male aged 14 years. Multiple nodules, probably caused by fungal infection on computed tomography scan

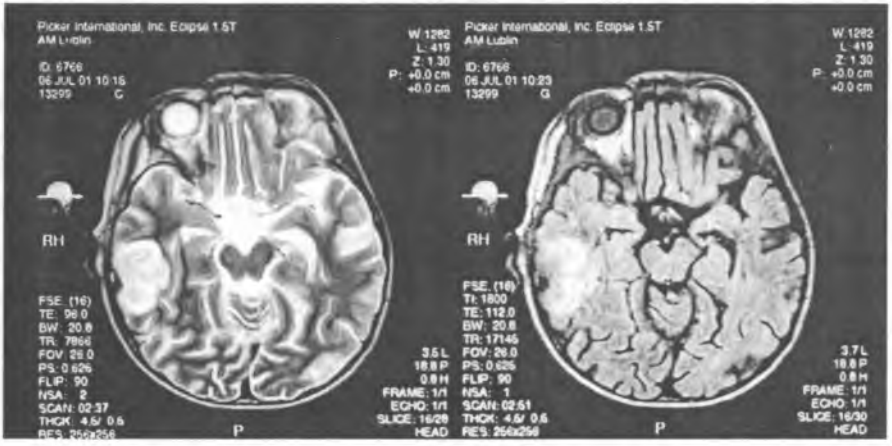

Fig. 3. The intracranial lesion, caused by fungal infection, on magnetic resonance image from a male aged 4 years

All the patients received intensive intravenous antifungal drugs (Amphothericin B deoxycholate as a loading dose of 2 mg/kg/day or liposomal formulations of amphotericin 5 mg/kg/day). During the antifungal therapy six of eight patients had a complete or partial response and they were able to continue aggressive chemotherapy according to treatment protocols of neoplasm. In all of them the regression of pulmonary nodules was observed in the control CT scans. Despite antifungal therapy out of eight patients, two presented progression (one child with brain fungal infection and one with massive pulmonary infection). These children died, and in postmortem examination they had evidence of invasive fungal disease with massive dissemination (in child with brain infection *Rhisopsus* species and in one with pulmonary infection *Aspergillus flavus*).

DISCUSSION

Most of the children cancers are highly chemosensitive. Therefore, intensive chemotherapy is administered to the majority of patients. Invasive therapy regimes are complicated by neutropenia ($< 0.5 \times 10^9$ cells/L). One of the most common complications is infection presenting as febrile neutropenia. One of the serious infections in immunocompromised patients is the deep fungal infection.

These infections are very refractory for treatment and are an important cause of death, so early diagnosis (CT or MRI) and aggressive therapy are warranted for patients with childhood cancers (7). High-risk patients should be treated for invasive fungal infections empirically, based on the clinical picture and radiologic findings alone, especially computer tomography (4). CT examination of patients with fungal infection also enable monitoring and modification of anti-fungal treatment (11).

Resolution of the infection and patient survival often depend on the rapid institution of effective antifungal therapy and reversal of immunosuppression. Since there are no proven prophylactic antifungal regiments in patients with prolonged granulocytopenia, the challenge is to effectively treat their fungal infections while continuing to treat their underlying malignancy with cytotoxic chemotherapy (8, 10).

CONCLUSIONS

1. The early diagnosis of fungal infection in neutropenic patients is important and increases overall response rates.

2. The pulmonary fungal infection should be considered in the differential diagnosis of solitary or multiple pulmonary nodules, particularly in immunocompromised patients.

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SUMMARY

Fungal infections have substantially increased in incidence over the past two decades, especially among patients with cancer who have received high doses of chemotherapy. Diagnosis is based on clinical observations, radiological and laboratory methods and molecular biological techniques. Early diagnosis is important and increases overall response rates, so high-risk patients should be treated empirically, based on the clinical picture and radiologic findings alone. The aim of the study was the analysis of the early clinical picture and radiologic findings of systemic fungal infections. The subjects of this study were patients with childhood cancers and fungal systemic infections. The early symptoms of fungal infection and the radiologic findings were analyzed. The systemic fungal infections were recognized in eight children, treated due to ALL – in four patients, AML – in two and NHL – in two. In all, manifestations of fungal infection were observed during bone marrow suppression secondary to chemotherapy treatment of neoplasm. In all, X-ray examination was normal. Radiological pulmonary changes were found in CT scans in seven patients, in one MRI showed marked abnormalities of the brain. All patients received intensive antifungal drugs, six patients had a complete or partial response and they were able to continue chemotherapy for treatment of neoplasm. The regression of pulmonary nodules was observed in the control CT scans. Progression of fungal infection was noticed in two patients, these children died. Conclusions: The early diagnosis of fungal infection in neutropenic patients is important and increases overall response rates. The pulmonary fungal infection should be considered in the differential diagnosis of solitary or multiple pulmonary nodules, particularly in immunocompromised patients.

Radiologiczna diagnostyka systemowych infekcji grzybiczych u dzieci w neutropenii

W ciągu ostatnich dwudziestu lat obserwujemy wyraźny wzrost częstości występowania infekcji grzybiczych, szczególnie wśród pacjentów onkologicznych otrzymujących wysokie dawki cytostatyków. Diagnozę infekcji grzybiczych prowadzimy na podstawie obserwacji klinicznej, badań radiologicznych i laboratoryjnych oraz techniki biologii molekularnej. Wczesne ustalenie diagnozy w sposób istotny poprawia wyniki leczenia, dlatego też pacjenci z grup wysokiego ryzyka powinni być leczeni empirycznie, jedynie w oparciu o obraz kliniczny choroby oraz odchylenia w badaniach radiologicznych. Celem pracy była analiza wczesnego obrazu klinicznego oraz zmian radiologicznych stwierdzonych u pacjentów z uogólnionymi infekcjami grzybiczymi. Badaniem objęto dzieci leczone z powodu chorób nowotworowych, u których stwierdzono uogólnioną infekcję grzybiczą. Przeanalizowano wczesne objawy kliniczne oraz zmiany radiologiczne. Systemową infekcję grzybiczą rozpoznano u ośmiu pacjentów, czterech z ALL, dwóch z AML i dwóch z NHL. U wszystkich dzieci objawy infekcji grzybiczej obserwowano w trakcie mielosupresji, będącej powikłaniem przeprowadzonej wcześniej chemioterapii. Nie stwierdzono żadnych istotnych nieprawidłowości w badaniach radiologicznym klatki piersiowej. Odchylenia w badaniu TK stwierdzono u siedmiu pacjentów, natomiast u jednego badanie MRI wykazało wyraźne zmiany w mózgu. Wszyscy pacjenci otrzymywali intensywne leczenie przeciwgrzybicze, u sześciu stwierdzono pełną lub częściową odpowiedź, co umożliwiło kontynuację leczenia przeciwnowotworowego. Regresję zmian płucnych obserwowano w badaniu TK. Progresję zmian grzybiczych stwierdzono u dwóch pacjentów, co było przyczyną zgonu. Wczesna diagnoza infekcji grzybiczej u pacjentów będących w neutropenii w istotny sposób przyczynia się zatem do poprawy wyników leczenia. Grzybicze infekcje płuc powinny być uwzględniane w diagnostyce różnicowej zmian płucnych, zwłaszcza u pacjentów będących w immunosupresji.