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Invasive Fungal Infection in Pediatric Oncology Department: A 10 Year Review

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Abstract

Background

Invasive mycotic infections are serious diagnostic and therapeutic problem in treatment of pediatric malignancies.

Objective

In our study we observed the occurrence of mycotic pathogens, colonization and invasive fungal diseases (IFD).

Methods

Seven hundred and seventy-seven patients (≤ 19 years of age) with malignancies were enrolled in this study. Two hundred and eleven (27.2%) patients were included in control group, five hundred and twenty-eight patients (68%) in group with colonization.

Results

C. albicans was obtained at initial colonization by more than 70%. During oncological treatment the occurrence of *C.non albicans* was increased rapidly (from< 25% to 49%). During the observed period a total of 38 out of 777 study patients developed probable and proven IFD (4.9%). Fungemia presented in 50 %, invasive organ mycosis in 36.8% of patients and disseminated disease in 13.2% patients. The most common pathogen of fungemia was *C. parapsilosis* (33%), of invasive organ mycosis localized in lungs was *Aspergillus* 59% (mainly *A. fumigatus*) and in disseminated diseases *P. lilacinus*.

Conclusion

In patients with IFD high presence of relapses (47%) and death (> 50%) were accomplished. Only 10% was related with IFD. We proved significantly poor chance of overall survival – OS (40%) and event free survival - EFS (27%) in group of patients with IFD. We suppose that current cause of poor outcome (OS,EFS) is due to high presence of relapses and deaths caused by oncological diseases in this group of patients.

Introduction

- Invasive fungal infections are major cause of morbidity and mortality in pediatric oncological patients with prolonged neutropenia following chemotherapy.
- Mortality of invasive fungal infections in children is still high and ranges from 15% to 85% caused by fungal pathogen and localization of the disease. These numbers are alarming, because the success of treatment of pediatric cancer diseases states more than 75%.
- The aim of our study was to analyze retrospectively the occurrence of mycotic pathogens, colonization and IFD; and their effect on survival in the file about 50% of all pediatric cancer patients in Slovakia for a period of 10 years
- To our knowledge, there has not been such a study conducted yet, which would have retrospectively evaluated an outcome of such a large number of pediatric oncological patients regarding the colonization by yeast and IFD during 10 years period.

Patients & Methods

I. PATIENTS AND PERIOD OF OBSERVATION

- The 777 pediatric consecutive patients (433 boys and 344 girls) aged 0.5 month to 18.9 years treated in our department due to hemato-oncological diseases and solid tumors were enrolled in the study.
- There were 198 (25%) patients who had Acute Leukemia, 125 (16%) patients with Lymphomas, 153 (20%) patients with Brain Tumors and 301 (39%) patients who had other malignancies including Sarcomas, Neuroblastomas, Nephroblastomas, Hepatoblastomas, Retinoblastomas and also rare tumors.
- Patients were divided into 3 groups. In the first group there were included patients who had initially diagnosed colonization with microscopic fungi or colonization acquired during treatment. The second group consisted of 38 patients with IFD regardless the presence of colonization. In third group (control group), patients without colonization and without IFD were enrolled.
- Period of observation was between January 1st, 2000 and December 31st, 2009.

II. DIAGNOSIS OF INVASIVE FUNGAL DISEASE

- **Microbiological diagnosis**
  At the time of the diagnosis of oncological diseases, we performed swabs of tonsil and nose for each patients. In each episode of febrile neutropenia we have repeatedly collected blood culture, swabs of tonsil, sampling urine and stool, swabs from the skin and mucosa. We sent sputum for mycological tests in case of cough. Since 2008 galactomannan antigen in serum in high risk patients during neutropenia have been tested regularly 2 times a week. Nucleic acid amplification by PCR has been tested as well.
- **Imaging**
  In the beginning predominantly chest X – ray was used in the diagnosis of pulmonary findings. Currently, HRCT of lung for diagnosis and as well as for therapeutic responses monitoring is used. In case of suspected involvement of the brain or sinus the CT scan or MRI is performed.
- **Invasive diagnostic methods**
  We did not indicate regularly bronchoalveolar lavage (BAL). The reason was the risk of the procedure and general anesthesia in patients with leukopenia and thrombocytopenia. Rarely we also performed a sinus and lung biopsy.

III. PROPHYLAXIS AND THERAPY:
During the period we have changed the approach for the antifungal prophylaxis and therapy according to international guidelines and recomandations in protocol for treatment of pediatric oncological diseases.

IV. DATA COLECTION
Data were collected from the medical records of patients and they were abstracted directly into a computer database.

V. STATISTICAL ANALYSIS
The statistical analysis was performed with commercially available computer software SPSS Statistics Professional. P values > 0.05 were considered statistically significant. Survival was evaluated using Kaplan Meier analysis.

Results

Table 1 **Baseline patient characteristics.**

Patients	Boys	Girls	Total	Age: average /median (months)	Relaps	Death
Group 1: Patients with colonization	**303**	**225**	**528 p. (67.9%)**	**95/86**	**97 p. (18,3%)**	**117 p. (22,8) %)**
Group 2 : Patients with IFD	**24**	**14**	**38 p. (4.9%)**	**111/114**	**18 p. (47 %) !**	**20 p. (52,6 %) !**
Group 3 – control group: Patients without colonization/IFD	**106**	**105**	**211 p. (27.2%)**	**128/149**	**21 p. (9,9 %)**	**20 p. (9,5%)**

Fig. 1 Spectrum of fungal pathogens in the period 2000 - 2009

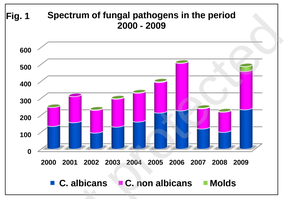
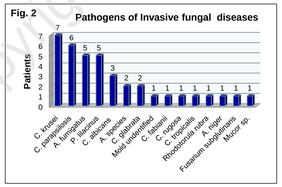


Fig. 2 Pathogens of Invasive fungal diseases



During 10 year period 4 252 culture positivity of fungi were isolated in which 97.8% were yeast and only 1.3% were molds.
Incidence of fungal colonizations rapidly increased during oncological therapy from 12.2% to 87.8% of patients with predominance *C. non albicans* (from< 25% to 49%) in gastrointestinal tract.
C. glabrata occured in 26%, *C. krusei* in 21%.

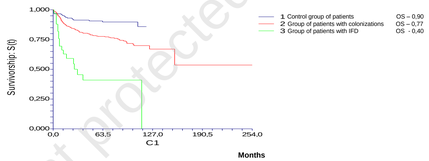
Out of the 38 invasive fungal diseases identified in pediatric oncological patients 22 (57.8%) were caused by yeast and 16 (42.2%) were caused by molds.
C. parapsilosis was the most common cause of Fungemia (33%), *Aspergillus* (57%) of IFD solid organs (mainly of lungs) and *P.lilacinus* for disseminated diseases.
In 59% of patients, who suffered from Invasive candidiasis, identical yeast were a cause of colonization and also IFD *(C.krusei 46,2% C.albicans 15%, C.glabrata 15%).*

Table 2 **Analysis of Invasive fungal diseases in pediatric oncological patients**

Type of IFD	Patients	Pathogens: Yeast	Pathogens: Mold	Colonization	Malignancies	Deaths: IFD	Deaths: Mal.
Fungemia	**19**	**C. albicans 3** **C. non albicans 15**	**P. lilacinus 1**	**C. albicans 1** **C. non albicans 7** **S. Cerevisiae 1**	**Ac. Leukemia 8** **NHL 2** **HD 1** **Solid tumors 8**		**13**
IFD of solid organs	**14**	**C. non albicans 3**	**Aspergillus 8** **Fusarium sub.1** **Mucor sp. 1** **Unidentified 1**	**C. albicans 1** **C. non albicans 3**	**Ac. leukemia 11** **NHL 2** **HD 1**	**3***	**3**
Disseminated IFD	**5**	**C. krusei 1**	**P. lilacinus 4**	**C. krusei 1**	**Ac. leukemia 4** **Osteo Sarcoma 1**	**1****	

Note: * Since 2005 no patient has died from IFD !, ** In autopsy Invasive Aspergillosiis was observed; however, not diagnosed during the life of patient (y.2003), NHL – Non Hodgkin Lymphoma, HD – Hodgkin Disease

Fig. 3 Comparison of the probability of overall survival in three groups of patients



5–year overall survival was 90% for patients in control group, 77% for patients with colonization and only 40% for patients with IFD. It is significantly higher mortality rate than patients who did not suffer with IFD and patients with colonization ($P < 0.01$).

Conclusion

- Our results showed that the prevalence of probable and proven IFD is low in pediatric cancer patients (4,9%).
- The prevalence of fungal colonization was found in 68% of all our patients, but only in 1.6% of patients the colonization caused IFD.
- We proved the state of oncological diseases was a major risk factor which affected survival in patients with IFD. Since only 4 out of 20 patients died from IFD as primary cause. Due to this fact risk stratification based on imunogenetics factors requires further exploration in the future.
- In high risk oncological patients there should be given special attention to knowledge of risk factors and its practical application. These patients benefit from prophylactic administration of antifungal agents and early empirical antifungal therapy.
- The results of our study show that the outcomes of patients with IFD-related mortality have improved significantly in the past years. This is partly due to the administration of new antifungal agents and the availability of new diagnostic modalities .

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