

Original papers

Difficulties associated with the diagnosis of mycosis of the oral cavity and throat in chronic lymphocytic leukemia (CLL)[1]

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ABSTRACT. Cases of fungal infections are being encountered more often in clinical practice. The factors associated with a high risk of mycoses include, among others, corticosteroidotherapy, the administration antibiotics with wide spectrum of antibacterial properties, neutropenia, neoplasms. Fungi may play a role in cancer formation, may act as a complication in the course of treatment, and may mimic a neoplastic process by giving a similar clinical picture. In the case of fungal throat infection, patients complain of increased body temperature, a general feeling of weakness, malaise, headache, spontaneous pain intensifying during swallowing, a feeling of an obstacle in the throat or a cough. A physical examination may reveal congestion of the mucosa followed by a unilateral crater ulceration often covered with fat, as well as a thick coating, which is accompanied by *foetor ex ore*. The submandibular and neck lymph nodes are often greatly enlarged and painful. These symptoms may resemble those associated with the neoplastic process and changes in the course of systemic diseases (agranulocytosis). A correct diagnosis in these cases is necessary for adequate therapy. Chronic lymphocytic leukemia (CLL) is the most common type of leukemia among adults in Europe and North America. It is estimated that in Poland, CLL affects approximately 1,400 people per year. In this paper, a case of 62-years old patient with CLL with fungal infection of oral cavity and throat is presented.

Introduction

Cases of fungal infections are being encountered more often in clinical practice [1]. The factors associated with a high risk of mycoses include, among others, immune deficiencies (primary, secondary immunodeficiency associated with deficiency nutrients and vitamins, as well as zinc/iron, cancer and autoimmune disorders, metabolic and endocrinal disorders, HIV infection, treatment with immunosuppressive and cytotoxic agents, contraceptive drugs); addictions; transplantation; hemodialysis; catheterization; parenteral nutrition; neutropenia ($0.1–0.5\times10^9$/l for less than 3 weeks); a low lymphocyte count ($<0.5\times10^9$/l, which is observed in the course of antibiotic therapy); corticosteroidotherapy (>1mg/kg and neutropenia $<1\times10^9$/l over a week, or >2mg/kg over 2 weeks), and the administration more than 2 antibiotics with wide spectrum of antibacterial properties [2,3].

Fungi may play a role in cancer formation, may act as a complication in the course of treatment, and may mimic a neoplastic process by giving a similar clinical picture [1].

The prevalence of fungal throat infection ranges from 39 to 66% and in most cases, are isolated strains of *Candida* (40–64.5%), but *Aspergillus*, *Saccharomyces cerevisiae* (11.6%) or *Penicillium* (10%) are also found less often [4].

In the case of fungal throat infection, patients complain of increased body temperature, a general feeling of weakness, malaise, headache, spontaneous pain intensifying during swallowing, a feeling

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of an obstacle in the throat or a cough. A physical examination may reveal congestion of the mucosa followed by a unilateral crater ulceration often covered with fat, as well as a thick coating, which is accompanied by *foetor ex ore*. The submandibular and neck lymph nodes are often greatly enlarged and painful [1].

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Chronic lymphocytic leukemia (CLL) is a lymphoma of low malignancy. It is characterized by clonal proliferation of mature lymphoid cells of B-type immunophenotype $CD19^+$/ $CD5^+$ /$CD23^+$/^{low} $Smlg^+$ (mostly μ or μ + δ, and λ or κ), with the absolute lymphocytosis of this sub-population being greater than $5x10^9$/l in the peripheral blood. This is the most common type of leukemia among adults in Europe and North America. It is estimated that in Poland, CLL affects approximately 1,400 people per year, at an average age of 72, with twice as many men as women being affected. Approximately three quarters of patients have no symptoms at the moment of diagnosis and while most of the patients survive for over a dozen years from diagnosis. Around 30% of patients die from other causes, including recurrent bacterial infections, and opportunistic invasions including fungal infections of the lungs and central nervous system, which constitute one third of the reported cases, especially among patients undergoing chemotherapy [5]. These complications are related to an impaired immune system, regarding both the cellular and the humoral immune response to the disease, as well as immunosuppressive drug treatment [6,7]. The incidence of infectious complications depends partly on the prescribed treatment; 89% of patients cure with fludarabine develop bacterial (78.5%), viral (12.5%), fungal or opportunistic infections (around 4.5%) [8,9].

In this paper, a case of fungal infection of oral cavity and throat in chronic lymphocytic leukemia is presented.

A case report

Patient E.W., 62-years old, was treated for CLL from 2002 to 04.2005 in the Department of Hematology, Medical University of Lodz. He received 6 cycles of therapy according to the scheme 2 CdA (2-chlorodeoksyadenozyne-cladrybinum) in 2003 and fludarabine in April 2005. In May 2005, he was consulted by the ENT Oncology Dispensary for a spontaneous pain in the throat, increasing during swallowing food; the examination revealed ulceration of the left tonsil by a local inflammatory process. A biopsy was taken and extensive necrosis was found in fragments of tonsil, however the nature of the change could not be clearly identified by a pathology examination (Study No. 13290).

On 05/30/2005, the patient was again admitted to the Department of Head and Neck Neoplasm Surgery, Medical University of Lodz for further diagnosis. On admission, extensive crater ulceration of the left palatal tonsil was found, with a perforation at the top of the palatoglossal arc and local inflammatory process. Due to the significant degree of inflammation, progression of changes and growing pains, Augmentin (1.0 gm twice a day) was administrated [10]. A biopsy was taken once more and chronic inflammatory infiltration and ulceration was described in the throat by pathology exam (Study No. 316438).

The patient was hospitalized again on 06/16/2005; during ENT examination, an ulcer covered with fetid, coating bloom was found in the niche of the left palatal tonsil, across the palatoglossal and palatopharyngeal arches. Once again, a biopsy was taken from the change, along with a swab for bacteriological mycological culture. Augmentin (1.0 gm twice a day) and Fluconazole (100 mg once a day) were given empirically [10]. Upon histopathological examination, tonsil was seen to demonstrate a high level of necrosis and abundant infiltration of neutrophils, as well as proliferation of B and T cells which didn't have destructive and invade influence on the epithelium; immunohistochemical staining did not permit the diagnosis of cancer (Study No. 317141). The cultures did not reveal a pathological flora.

The patient was admitted to the Department of Head and Neck Neoplasm Surgery, Medical University of Lodz for the third time on 07/05/2005; he complains of worsening throat pain radiating to the ear, higher difficulties in food intake and *foetor ex ore*. Ulcer in the left tonsil, the destruction of the palatoglossal and palatopharyngeal arches, spreading on the soft palate and the gum on the left. Swabs were taken for mycological examinations and sent to the Department of Biology and Medical Parasitology, Medical University of Lodz. Analgesia with antifungal therapy (Fluconazole 100 mg once a day and nystatin 100.000j./5 ml

suspension applied topically) were used [10]. Reduction of pain was achieved, but there was a further progression of local changes; ulceration covered the lateral part of the tongue, mouth floor and buccal mucosa on the left. Mycological examination was negative; no fungal growth was observed. The patient was consulted at the Department of Hematology; background of leukemic changes were exluded. On 08/03/2005, the patient was delivered to the Department of Hematology and qualified for empirical treatment with Amphotericin B (1 mg/kg) and Heviran (5 mg/kg – 3 times a day) [10]. During treatment there was improvement of the local state of the healing qualities of change and further reduction of the pain. On 08/19/2005, the patient was discharged and prescribed Orungal (100 mg twice a day) [10]. On 08/31/2005, the patient was examined by an ENT specialist, who noted a complete regression of the changes found in the throat as well as persistent ulceration of the lateral part of the tongue and floor of the mouth on the left side; antifungal therapy was maintained. After a further 7 days these symptoms decreased; Orungal administration was prolonged (100 mg per day). After a further 5 weeks of treatment, a control examination showed only a small ulcer in the sublingual area covered by fibrin with a tendency to healing. The current treatment was maintained for another 2 weeks. At next control examination 2 weeks after discontinuing treatment, the patient complained of recurrence of pain. The examination found deep ulceration of the left cheek and floor of the mouth. Orungal (100 mg twice a day) was ordered again. After 2 weeks of treatment, further progression of lesions was observed. Treatment was continued. In a control examination (12/14/2005) after 3 weeks of treatment, progressive healing of the cheek and floor of mouth and the left hand bottom surface of the tongue were seen, as well as inflammatory infiltration in the posterior pharyngeal wall penetrating into the nasopharynx. The patient was sent to the hospital and was admitted to the Department of Head and Neck Neoplasm Surgery, Medical University of Lodz on 19/12/2005. During admission, a scar in the buccal mucosa was seen below the palatal tonsil and the left hand side of the floor of the mouth; an inflammatory infiltration covered with scanty, easily separating deposits was also seen in the right hand side of the bottom of the mouth, as well as massive, fetid deposits on the posterior wall of the middle and upper pharynx. Swabs from the mouth and throat for mycological examination, along with 2-fold blood cultures for the presence of fungi and a biopsy from the bottom of the mouth for histopathological examination were taken. *Candida albicans* was cultured from the oral swab, and *Candida glabrata* from the throat; blood culture did not reveal any fungus. Pathology examination (Study No. 323543) showed fragments of tissue with the presence of abundant inflammatory granulation tissue and texture of the mycelium (Study No. 316438).

The patient was hospitalized again on 01/03/2006. During admission, a number of changes were presented: ulcerative changes covered with fetid coating covering the bottom of the mouth, the lower surface of the tongue, right edge of the tongue, tonsillar niches on both sides, the tongue, the right side of the soft palate with its immobilization and the nasal part of the throat. The nose, lower throat and larynx were unchanged. The patient was in a good condition. A number of tests were performed: chest radiograph, CT scan of the brain, face and neck as well as abdominal ultrasound. Stool swabs were taken from changes for fungi and mycogram, as well as repeated blood tests for the presence of anti-HIV antibodies.

In all cultures, *Candida glabrata* sensitive to 5-fluorocytosine and amphotericin B was detected. Anti-HIV antibodies were not found. No changes were observed in the CT scan of the abdominal cavity, paranasal sinuses or CNS; a large number of 10 mm lymph nodes were seen, bilaterally in the submandibular area. Also extensive infiltration of the posterior and lateral walls of the oral and nasal parts of the pharynx, soft palate, tongue, floor of the mouth on the right side, and the piriform recess on the right side, spread to a height just above the upper contour of the thyroid cartilage on the right side were seen; infiltration of visible gas bubbles was noted in numerous places (J. Pawlikowska, MD).

From 01/06/2006 to 02/03/2006, the patient stayed in the Department of Infectious Diseases and Hepatology in order to further treatment; the diagnosis being gangrenous bacterial and fungal infection of the mouth floor. During hospitalization, mycological and microbiological examinations were performed on samples from the throat and mouth and *Candida glabrata*, *Candida krusei*, *Candida albicans*, *Streptococcus viridans*, *Enterobacter cloacae*, *Bacteroides* spp., *Staphylococcus epidermidis* and methicillin-resistant *Enterococcus feacalis* were detected. Fluconazole (100 mg twice a

day), Ketoconazole (100 mg twice a day), Amphocil (0.2 mg/kg), Metronidazole (500 mg 3 times a day), Proxacin (500 mg twice a day), Amikacin (500 mg 3 times a day) and Lakcid (2 ampoules twice a day) were administered [10]; transfusion of 2 packed red blood cells units were also performed due to anemia (Ht–19.5%, Hb–6.3 g%, E–2260000/ml).

Significant improvement in the patient's condition was achieved and he was discharged with a prescription of Ketoconazole (100 mg twice a day), Doxycyclin (100 mg twice a day), Chlorchinaldin (4 lozenges/day) and instructions to rinse the mouth with a solution of potassium permanganate and hydrogen peroxide [10]. After a month, the patient reported to the Policlinic of Otolaryngology and Phoniatrics, Oncology Cancer Center, for a control examination, during which re-progression of lesions were found. The patient was sent to the Department of Infectious Diseases, where unfortunately no data on the follow up exists. The patient died due to exacerbation of underlying disease in April 2006.

Discussion

In the case of unilateral ulcerative lesions of the palatine tonsil, especially with a tendency towards rapid progression, a fungal etiology should be considered after cancer is excluded, despite any negative results that might exist for mycological smears. The use of intensive and prolonged treatment with antifungal agents is necessary, despite the regression of local changes. The widespread use of Fluconazole, both in treatment and in antifungal prophylaxis, may be a factor in the prevalence of infections by fungal species including *Candida glabrata* and *Candida krusei* naturally resistant to this drug [4,11].

The patient described in this paper required multiple repeated smears and biopsy of pathological changes in order to confirm fungal infection. The clinical picture initially suggested a change of malignancy. The cause of the changes in the adenoid was suspected to be leukemia. The clinical course, however, did not match any of the above etiologies. The application of empirically antifungal therapy with subsequent improvement made it possible to make a definitive diagnosis and subsequently confirmed the positive result of the culture and pathology examinations; it allowed also the proper therapy to be administered.

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