One Case of Candidemia Developed after Surgery for Tongue Cancer in a Young Adult

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(Received August 21, 2009; Accepted November 10, 2009)

Candidemia is an opportunistic infection caused primarily by Candida albicans. We experienced a case of severe Candidemia that developed after surgical treatment for tongue cancer and required considerable labor to diagnose and to treat, though no particular immunodeficiency was seen before. The case was resistant to an antifungal agent, fluconazole, but was successfully treated with amphotericin B. Positive blood cultures, local wound culture, and increased β-D-glucan were useful to diagnose the infection. In particular, gallium-67 scintigraphy was remarkably useful for the diagnosis and the evaluation of therapeutic effects in this case. Development of Candidemia following an oral and maxillofacial surgery is extremely rare among young adults, thus this case report serves to draw attention to the risk in oral and maxillofacial surgery.

Key words: Candidiasis, Tongue Cancer, gallium-67 scintigraphy

INTRODUCTION

Invasive mycosis, an infection that develops in individuals with compromised host immunity as in a granulocytopenic state, is very unlikely to occur in the oral region in view of the anatomical structure. In recent years, extended resection for oral cancer and subsequent restoration, combined medications with antitumor drugs, and postoperative control via the central venous catheter have been increasingly used for head and neck region. As a result, the incidence of postoperative infections has also been increased. The most of these postoperative infections are, however, caused by oral anaerobic bacteria, aerobic gram-negative bacillus, and aerobic gram-positive coccus, while there are extremely limited cases of infections in which fungi are detected as the main pathogen. This article reports a case of deep mycosis which was caused by Candida albicans after the surgery for the tongue cancer in a young adult male with no particular underlying disease. Candidiasis as well as aspergillosis and cryptococcosis is a frequently reported deep mycosis. Among pathogens of deep candidiasis, Candida albicans exists in the mouth and gastrointestinal tract as normal flora, and is reported to be often present in oral diseases. Candida infection is known to be induced by postoperative wound, decrease of gastric acid due to the use of H2 blocker, tracheostomy opening, catheterization, and disruption of the mucosal barrier caused by the gastrointestinal tract surgery. This case developed a fever 25 days after the total resection of the tongue and the restoration with free muscle cutaneous flap (i.e. on day 25), and the condition did not respond to an antibacterial agent. Based on the results of blood culture and wound culture, the patient was diagnosed as having deep-seated mycosis caused by Candida albicans. In addition to the diagnosis, choice of the antifungal agent and determination of the timing to discontinue the therapy were important for the treatment. As an imaging used for this case, gallium-67 scintigraphy was so effective that very specific image findings were obtained. This article aims to draw your attention to the risk of deep-seated mycosis which develops after the surgery of oral cancer, and to report the meanings of the diagnosis based on blood test and imaging.

CASE REPORT

A male aged 20 who noticed a swelling of his tongue 2 weeks before visited our department. Oral examination revealed a mass on the left side of the radix linguae.

He was diagnosed as having squamous cell carcinoma after biopsy. Magnetic resonance images (T2 weighted images) were obtained, which showed a mass sized 45 × 35 × 30 mm in the radix linguae (Fig. 1). Total resection of the tongue, bilateral neck dissection, and restoration with free flap of the rectus abdominis were performed under general anesthesia. On Day 2, the central venous catheter was immediately removed. On day 7, local infection was found in the neck, which was then treated by drainage. In the abscess culture, Streptococcus intermedius and Pseudomonas intermedia were detected. During the surgery, 2 g/day of cefmetazole was used as an antibacterial agent. On day 18, he had a fever of 38.5°C (Fig. 2), then the dosing of panipenem/betamipron 1.5 g/day started. In spite of the administration of panipenem/betamipron, the
Fig. 1 Preoperative magnetic resonance image (T2 weighted image). A mass sized 45 × 35 × 30 mm was found in the radix linguæ.

Fig. 2 Transitions of the body temperature, β-D-glucan, and white blood cell.

CMZ: cefmetazole   PAPM/BP: panipenem/betamipron
FLUC: fluconazole   AMPB: amphotericin B
fever continued. On day 22, the fever was still 38°C. *Candida albicans* was detected in the wound culture, the sputum examination obtained through the tracheostomy opening, and the blood culture. β-D-glucan was 145.7 pg/ml. Administration of fluconazole 400 mg/day was started, but the fever reached 40°C on day 35, and *Candida albicans* continued to be detected in the blood culture. White blood cell count decreased to 2900/μl, leading to a granulocytopenic state. The fluconazole therapy was judged as failure because the β-D-glucan elevated to 544.6 pg/ml, and the administration of amphotericin B (35 mg/day to 50 mg/day) started. Although the wounded and tracheostomy areas had been smoothly healed, pneumonia and endophthalmitis had not developed, we performed the gallium-67 scintigraphy in attempt to search the focus of infection since the high level of β-D-glucan and fever were still present. The results revealed a hepatomegaly and accumulations of gallium-67 in the skull, sternum, pelvic bone, and both femurs. Especially, the hepatomegaly and a possible microabscess were suspected to be the focus of the infection (Fig. 3A). On day 40, the fever declined to 37.1°C. On day 50, the alternate-day dosing of amphotericin B was started. On day 69, the gallium-67 scintigraphy was performed, but no abnormal accumulation was found, so we discontinued the administration of amphotericin B (3000 mg in total) (Fig. 3B). β-D-glucan was 126.7 pg/ml. He was discharged on day 94. For 6 years after the surgery, there has not been any recurrence/metastasis of the tongue cancer or relapse of candidemia.

**DISCUSSION**

The protective mechanisms against mycosis are classified into the neutrophil-mediated immunity and the cell-mediated immunity. The main protective mechanisms against *Candida albicans* are neutrophil-mediated immunity [1]. Therefore, decrease and hypoactivity of the neutrophil, especially the granulocyte, caused by various factors contribute to the onset of candidiasis, and correlate with vital prognosis. A researcher reported that Candidemia with decreased neutrophil count can be successfully treated with granulocyte colony stimulating factor (G-CSF) [2]. This case showed a granulocytopenic tendency during the course of treatment, but the tendency did not initiate a fatal condition. On the other hand, the role of the cell-mediated immunity in Candidemia has also been discussed recently. The response of the T helper 1 cell (Th1) facilitated by interferon-γ (IFN-γ) and interleukin-12 (IL12) which are produced when the helper T cell (Th) is activated by fungi may reportedly have a protective function against invasive candidiasis [3].

Deep mycosis can be treated with antifungal medication, and for patients with abscess, surgical intervention is also effective. In this case, *Candida albicans* was first detected in the wounded and tracheostomy areas, but these were smoothly healed in spite of candidemia, thus we considered it as colonized fungi, and did not suspect these areas as the source. Moreover, the catheter had been removed, and any gastrointestinal tract hemorrhage, intraabdominal infection, or lung lesion was not seen. Thus, gallium-67 scintigraphy was performed.

Since gallium-67 strongly accumulates in the malignant tumor tissues, especially of breast cancer, lung cancer, and malignant lymphoma, it is widely used as a malignancy diagnostic modality in clinical practice [4].

For inflammatory lesions such as pneumonia,
tuberculosis, and osteomyelitis, gallium-67 is useful to determine the presence, location, and extent of the inflammatory foci, and for the evaluation of therapeutic effects and the follow-up.

In this case of Candidemia, gallium-67 scintigraphy was conducted, and accumulations of gallium-67 were shown in the skull, sternum, pelvic bone, both femurs, and liver. The accumulations of gallium-67 in these bones were considered as accumulations not to the inflammatory foci, but to activities of the peripheral medulla.

Gallium-67 binds to the transferrin, an iron-binding protein, in the blood, and its kinetics is similar to that of iron.

This suggests that the transferrin receptor may be facilitated in the bone marrow.

As the neutrophil was exhausted due to the infection, the peripheral bone marrow may have also been mobilized.

Accumulation in the liver suggested the possibilities of hepatomegaly, microabscess, and extramedullary hematopoiesis.

These results indicated that Candida albicans inoculated from the cervical lesion might have formed microabscess in the liver, initiating the sepsis. It has been known that the abscess formation is very limited when the granulocytes are decreased, but is manifested along with the increase of the neutrophils. Amphotericin B was chosen because we thought that a stronger antifungal therapy was required.

Amphotericin B disrupts the fungal cell’s membrane by binding to the ergosterol on the membrane. [5] Although amphotericin B has a fungicidal effect, it may cause severe adverse reactions such as renal dysfunction, thus adequate clinical care should be taken for the medication. On the other hand, fluconazole, an Azonol antifungal agent, inhibits the ergosterol synthesis by blocking sterol 14- demethylating enzyme [5]. However, fluconazole only suppresses fungal proliferation, and has no fungicidal effect. Moreover, since the effect is significantly influenced by the host factors, the drug does not always contribute to the treatment in many cases with serious infections.

In this case, fluconazole therapy failed, and amphotericin B therapy succeeded. However, the decision of when to discontinue the amphotericin B was difficult.

It is known that renal dysfunction frequently develops during the treatment with amphotericin B, and the incidence is correlated with the total dose. Therefore, we wanted to avoid unnecessary dosing as much as possible. However, β-D-glucan could not be used as an indicator because it was constantly over 100 pg/ml. Thus, we decided the discontinuation of amphotericin B, based on the clinical symptoms and without complications [6].

There has never been a report of the Candidemia developed after the surgery of the oral cancer. In this case, we thought that the Candida albicans which was selected through the antibacterial medication might have been inoculated into the liver or other distant lesions via wound, tracheostomy area, in view of the following facts:

(1) the onset was on or after the postoperative day 25;
(2) the condition did not improve even after the local infections were relieved; and
(3) the systemic application of the antifungal agent was effective.

Some immunologic abnormality was suspected, because this was a rare case of tongue cancer in a person aged 20, and the patient was under the postoperative compromised condition. It should be stressed that enough attention must be paid in the preoperative and postoperative management of young patients with carcinoma as this case, because the patient may be highly facilitated in a compromised host-specific manner.

REFERENCES