Fatal Candida Septic Shock During Systemic Chemotherapy in Lung Cancer Patient Receiving Corticosteroid Replacement Therapy for Hypopituitarism: A Case Report

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Invasive candidiasis has increased as nosocomial infection recently in cancer patients who receive systemic chemotherapy, and the timely risk assessment for developing such specific infection is crucial. Especially in those concomitantly with hypopituitarism, febrile neutropenia with candidiasis can cause severe stress and lead potentially to sudden fatal outcome when the temporal steroid coverage for the adrenal insufficiency is not fully administered. We report a 72-year-old male case diagnosed as non-small-cell lung cancer, Stage IIIA. He had received a steroid replacement therapy for the prior history of hypophysectomy due to pituitary adenoma with hydrocortisone of 3.3 mg/day, equivalent to prednisolone of 0.8 mg/day. This very small dosage of steroid was hardly supposed to weaken his immunesystem, but rather potentially led to an inappropriate supplementation of his adrenal function, assuming that the serum sodium and chlorine levels decreased. On Day 6 of second cycle of chemotherapy with carboplatin and paclitaxel, he developed sudden febrile neutropenia, septic shock and ileus, leading to death. After his death, the venous blood culture on Day 7 detected Candida albicans. Autopsy findings showed a massive necrotizing enterocolitis with extensive Candida invasion into submucous tissue. In conclusion, this case may suggest that (i) immediate initiation of antifungal therapy soon after the careful risk assessment of Candida infection and (ii) adequate administration of both basal steroid replacement therapy and temporal steroid coverage for febrile neutropenia might have improved his fatal outcome.

Key words: lung cancer – adrenal insufficiency – necrotizing enterocolitis – candidemia – chemotherapy

INTRODUCTION

Febrile neutropenia (FN) is one of the most problematic adverse events that occur during systemic chemotherapy in the solid malignancy (1,2), because it sometimes causes fatal septic shock. Some patients develop FN by the bacterial infection following the invasion of bacteria through the intestinal wall and damaged directly by systemic chemotherapy, whereas FN following the fungal invasion into the intestine is rare with ~3% (3).

In the latter situation, The mortality rate of FN related to intestinal fungal infection is reported as high as 81.8% (3). These indicate the need of early detection of high-risk patients potentially with fungal infection and then immediate initiation of antifungal treatment in the case of developing FN.

Especially in patients with hypoadrenalism, FN sometimes causes a severe stress leading to severe hemodynamic instability associated with the adrenal failure. Thus, in this situation, appropriate and adequate corticosteroid replacement therapy

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should be given for them to prevent severe and refractory hypotension caused by relative adrenal insufficiency (4).

We describe here a case of non-small-cell lung cancer (NSCLC) developing a fetal septic shock caused by candidemia related to intestinal and colonic mucous damage during systemic chemotherapy, under quite low dose corticosteroid replacement therapy for hypopituitarism.

CASE

A 72-year-old male was referred to our department because of a mass shadow in the right upper field in his chest radiograph. He was a current smoker with Brinkmann index of 1600, and his performance status was 1 with dyspnea on effort due to severe chronic obstructive pulmonary disease (COPD). He had a history of hypophysectomy due to pituitary adenoma. Post-operative reduced pituitary function has made him under the continuous low dose corticosteroid replacement therapy with hydrocortisone at a dose of 3.3 mg/day which was equivalent to prednisolone 0.8 mg/day. No remarkable physical findings were reported. Laboratory findings revealed that the platelet count decreased slightly (11.4 × 10^9/μl). Liver enzyme levels were abnormal with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of 67 and 43 U/l, respectively. Both serum sodium and chlorine levels were severely decreased by 123 and 91 mEq/l, respectively. Serum tumor markers were elevated with cytokeratin 19 fragment and squamous cell carcinoma antigen of 19.5 and 11.9 ng/ml, respectively. Serum cortisol level was decreased to 2.0 μg/dl, whereas serum aldosterone, adrenocorticotropic hormone (ACTH) and renin levels were under the normal range. Pulmonary function test was abnormal with vital capacity (VC), %VC, forced expiratory volume (FEV) 1.0, % FEV 1.0 and FEV 1.0% of 1.18 l, 58%, 0.62 l, 29.4% and 32.5%, respectively. Radiologically, the chest computed tomography (CT) scan showed a mass of 40 mm in diameter with two nodules of 15 mm each in the right upper lobe and the lymphadenopathy in the site of #10R. All the abnormal shadows were accompanied with a significant F-18 fluorodeoxyglucose (FDG) uptake in the Positron emission tomography (PET) scan (Fig. 1).

Figure 1. Radiological findings on admission, (A) Chest radiograph revealed a mass shadow at the right upper lung field. (B and C) Both chest CT and PET scans detected a primary tumor and pulmonary metastases in the right upper lobe, and ipsilateral hilar lymphadenopathy.

Bronchoscopy was performed to evaluate these mass and nodules on chest CT. The transbronchial biopsy detected squamous cell carcinoma, and he was finally diagnosed as lung squamous cell carcinoma cT3N1M0, cStageIIIA. The tumor possessed neither epidermal growth factor receptor gene mutation nor echinoderm microtubule associated protein like 4-anaplastic lymphokinase rearrangement. Because chemoradiotherapy was considered to be contraindicated for him whose pulmonary function revealed severe restrictive and obstructive ventilator impairment due to COPD with severe emphysema, systemic chemotherapy alone with carboplatin (CBDCA: area under the curve of 5 on Day 1) and paclitaxel (PCT: 200 mg/m² on Day 1) was undergone in the inpatient setting. On Day 8 from the initiation of chemotherapy, the laboratory findings showed pancytopenia with severe neutropenia (Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0); Grade 4, absolute neutrophil count 0/μl) and febrile neutropenia (Grade 3). He immediately received antibiotic therapy with cefepime and granulocyte colony stimulating factor (G-CSF) for 5 days, which resulted in the rapid improvement of all adverse events. The tumor was shrunk by 21% after first cycle of the chemotherapy according to the response evaluation criteria in solid tumor version 1.1.

After his temporary stay at home for several days, we administered the second cycle of the chemotherapy on the Day 31 of the first cycle. The dose was reduced by 30% (CBDCA AUC of 3.5 and PCT 140 mg/m²) because of the febrile neutropenia in the prior cycle. On Day 6 of the second cycle, he developed CTCAE v4.0; Grade 4 neutropenia, and had an increasing sense of abdominal fullness. Abdominal CT on that day showed dilated and fluid-filled loops of esophagus through bowel. The ileus tube was inserted to the intestine. On Day 7 of the second cycle, he developed a sudden hemodynamic instability with refractory hypotension possibly following septic shock by FN (absolute neutrophil count of 0/μl). Then, he was transferred to intensive care unit and underwent continuous renal replacement therapy and mechanical ventilation. After that, in order to decompress intestine and bowel, the total colonoscopy was performed to insert transanal tube. It showed the discolored colonic mucosa into
dark green, ulceration, and lead-pipe appearance (Fig. 2). Unfortunately, all these intensive treatments did not work well for his condition, and finally he died on Day 9 of the second cycle. Autopsy was performed, which revealed the ulceration necrosis in the colonic mucosa with massive *Candida* invasion. After his death, both sputum culture and venous blood culture examined on Day 7 also detected the presence of *Candida albicans* (Fig. 3).

Autopsy revealed that erosion and hemorrhage were observed on the sigmoid colonic mucosa 30 cm from the anus. The mucosa in the sigmoid colon through the ileum was discolored into dark green. In the microscopic findings, all of layer in this discolored mucosa showed necrosis. The multiple ulcers with massive *Candida* invasion were also observed in the mucosa of esophagus, colon and trachea. Especially in the cecum, *Candida* spread into submucous.
tissue and invaded submucous vessels without neutrophil infiltration. Thrombus which causes ischemic and necrotizing enterocolitis was not observed in mesenteric artery (Fig. 4).

**DISCUSSION**

Invasive candidiasis is increased substantially as nosocomial infection in hospitalized patients with cancer, mainly located in the genitourinary tract, gastrointestinal tract and head and neck, but rarely in lungs (5). So this is a rare case report of a lung cancer patient who developed acute lethal septic shock with *Candida* infection following the chemotherapy-induced non-occlusive ischemic enterocolitis in the neutropenic phase.

One of the potential causes for his fatal clinical course in spite of very small dosage of corticosteroid therapy would be associated with the issue as to whether the decision to initiate the empiric antifungal therapy should have been done in such situation. National Comprehensive Cancer Network guideline suggests that patients with abdominal pain, perirectal pain and diarrhea are susceptible to *Candida* bloodstream infection because mucosal damage induced by cytotoxic therapy and neutropenia became the potential entry site of this pathogen, and consider antifungal treatment (6). The frequency of invasive fungal enterocolitis with neutropenia reported 19% in the autopsy cases, whereas the most important pathogen of infectious enterocolitis in the neutropenic phase is gram negative bacilli (7). *Candida* was reported in 94% of the all fungal enterocolitis related to the neutropenic fever (3). The risk factor of *Candida* infection is reported to be a pre-treatment gastrointestinal *Candida* colonization, an administration of broad spectrum antibiotics, parenteral nutrition, and use of cytotoxic agents (8) Indeed, this case had several of these risk factors for the *Candida* infection, which should have prompted us to administer antifungal therapy as well as other supportive treatments for FN immediately.

Another cause for fatal clinical course in this case would be associated with a potential hypoadrenalism after hypophysectomy due to pituitary adenoma. In such situation like him, the corticosteroid replacement therapy was needed to complement reduced ACTH secretion due to secondary to hypopituitarism usually with hydrocortisone at a dose of 15–25 mg/day (4,9). The average daily secretion of cortisol in healthy adults is 2.7–14 mg/m²/day (10), which is equivalent to 5–25 mg/body of hydrocortisone. Assuming that the physiological cortisol would be inappropriately excreted in those who underwent hypophysectomy, such dose of steroid replacement therapy may not make those receiving the therapy immunocompromised host.
Thus, his daily dosage of hydrocortisone (3.3 mg/day) did not seem to be enough to make him an immunocompromised host; rather, it might not completely have complemented his poor endocrinological function because of hypophysectomy, assuming that both pre-treatment serum sodium and chlorine levels decreased. Thus, some further assessments for the suitability of the baseline dose of hydrocortisone in this case might have been warranted.

In addition to this maintenance steroid replacement therapy, temporal steroid coverage is sometimes proposed to be given for patients with the adrenal insufficiency. He indeed received short-term dexamethasone therapy for the prevention of allergic reaction and emesis potentially induced by the chemotherapy. This might have also been partly effective for preventing adrenal crisis as so-called transient steroid replacement therapy. A prospective randomized study to address the potential influence of low dose steroid therapy on prognosis in septic shock patient showed that their mortality rate was related to the degree of elevation in the serum cortisol level in response to the ACTH loading test (11). That is, a decrease in the ability of additional corticosteroid secretion in the severe stress could accelerate the risk of death. Another study reported that in septic shock patients with relative adrenal insufficiency, an immediate treatment with hydrocortisone and fludrocortisone clearly reduced the 28-day mortality rate (12). Based on these reports, further discussion as to whether or to what degree the temporal steroid coverage would have been needed soon after he developed Grade 4 neutropenia, possibly yielding severe physical stress for the patient with hypopituitarism.

In conclusion, we reported here a case of NSCLC developing a fatal septic shock caused by candidemia related to the intestinal and colonic mucous damage during the systemic chemotherapy, under the inappropriate corticosteroid replacement therapy for hypopituitarism.

Conflict of interest statement
K.H. has received honoraria from Eli Lilly Japan, Pfizer, and Chugai Pharmaceutical. The other authors had no conflict of interest to be declared.

References