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How to cite this paper: Baron, M.V., Scherer, G.D.L.G., Korzenieski, C.R.M., da Silveira, J.B., Soares, C.B., Marangoni, C., de Mello Pinto, M.V., Sampaio, A.R., Sancho, A.G., Pacheco, E.F., Picariello, F., Ott, J.N., Reinheimer, I.C., Pinheiro, C.G., Iketani, N.K.P., Brandenburg, C., de Mello Florentino, D., Meyer, P.F. and da Costa, B.E.P. (2021) Non-Hodgkin's Lymphoma Associated with Metastatic Lung Cancer: Case Report. *Advances in Lung Cancer*, 10, 40-47.

<https://doi.org/10.4236/alc.2021.103004>

Abstract

Lymphomas are neoplastic transformations that affect lymphoid cells. Diffuse large B-cell non-Hodgkin's lymphoma has a high degree of cell proliferation, accounting for 30% of all lymphomas. Lung cancer is the leading cause of death worldwide and the recommended treatment is chemotherapy. Among the main complications resulting from non-Hodgkin's lymphoma, lung cancer and chemotherapy used in their treatment, we can mention sepsis, acute kidney injury and febrile neutropenia. Febrile neutropenia can occur by suppressing the production of neutrophils. Sepsis, a widespread infection, is the main cause of acute kidney injury, which can also be caused by hydroelectro-

Received: May 26, 2021

Accepted: August 7, 2021

Published: August 10, 2021

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lytic complications or by nephrotoxicity. This is a report of a smoking patient with metastatic lung cancer who sought care due to progressive dysphagia, cough with chest pain, fever, and lower airways critical obstruction due to mediastinal lymphadenopathy, being diagnosed with diffuse large B-cell non-Hodgkin's lymphoma. The patient evolved to death because of a significant worsening of the ventilatory pattern of multifactorial cause, mainly due to sepsis, acute kidney injury, and febrile neutropenia. The patient had mostly classic characteristics of her comorbidities, however, the overlapping of interrelated comorbidities led to the outcome of death. What is unusual about the present case report is that the patient's characteristics, such as age, sex, and ethnicity, are opposite to those described as risk factors for diffuse large B-cell non-Hodgkin's lymphoma.

Keywords

Acute Kidney Injury, Febrile Neutropenia, Sepsis, Chemotherapy

1. Introduction

Lymphomas can be defined as neoplastic transformations that affect lymphoid cells and are divided into Hodgkin's lymphomas and non-Hodgkin's lymphomas (NHL). In addition, lymphomas can be classified as having low or high degrees of cell proliferation. High degree lymphomas have large cells, localized lymph node enlargement, high aggressiveness, and low survival if left untreated. Among high degree lymphomas is diffuse large B-cell non-Hodgkin's lymphoma (LNHDGCB), responsible for approximately 30% of all lymphomas [1]. The symptoms of NHL include lymphadenopathy, fever, night sweats, weight loss, muscle atrophy, spontaneous pain, progressive choking dysphagia, severe oropharyngeal dysphagia, and diffuse abdominal pain [2] [3] [4] [5].

Lung cancer is currently the leading cause of death worldwide in men and women [6]. Its symptoms include cough, recurrent pneumonia, dyspnea, chest pain, hoarseness, dysphagia, arm or shoulder pain, weight loss, anorexia, and fatigue [7]. These symptoms usually appear in more advanced stages of the disease, so lung cancer is usually diagnosed when the disease has progressed locally or systemically [8]. The recommended treatment is chemotherapy, a treatment that can cause side effects in many systems, especially in the gastrointestinal system [5]. Chemotherapy can induce tumor necrosis due to osmotic rupture of healthy lung cells [9], besides causing acute kidney injury (AKI) and febrile neutropenia [10] [11].

Among the main complications resulting from the NHL, lung cancer, and the therapies used in their treatment, we can mention sepsis, AKI and febrile neutropenia. Sepsis is a widespread infection that affects mainly cancer patients [12], and 60% of the patients who have sepsis are affected by AKI [13]. AKI in critically ill patients occurs mainly due to sepsis, but it can also happen due to hy-

droelectrolytic complications associated with NHL [14] or due to nephrotoxicity of chemotherapeutic agents [15]. Its most common symptoms are anuria, swelling, nausea, vomiting, dyspnea, and anemia, and it can also be asymptomatic [16]. Febrile neutropenia can occur because of the suppression of neutrophil production caused by chemotherapy, decreasing the signs and symptoms of infections' response [17]. Fever may be the only indication of febrile neutropenia [17].

We present the report of a smoking patient with metastatic lung cancer who sought care for progressive dysphagia with choking, cough with right chest pain, fever, and lower airways critical obstruction due to mediastinal lymphadenopathy, being diagnosed with LNHDGCB. The patient died due to significant worsening of the ventilatory pattern of multifactorial cause, mainly due to sepsis, AKI, and febrile neutropenia. The patient was recruited, had given her consent for the case report to be published, and accepted to participate in a research carried out in the ICU with CAEE number: 91988318.6.0000.5336-Brazil. The case is reported here for sharing with colleagues.

2. Case Report

Female, Brazilian, married, black, 59-year-old patient, smoker, diagnosed with lung cancer with bone metastasis and marked necrosis, with a History of 3 consecutive hospitalizations. First, she was referred from the basic health unit to the hospital due to progressive dysphagia with choking, cough with chest pain on the right, and fever. She arrived with a report card noting microcytic anemia and mediastinal enlargement. Then, a chest tomography (CT) was performed, which showed an expansive image, possibly related to a lymph node conglomerate with more central areas of necrosis in the mediastinum and transition to the cervical region, with a larger axial diameter of up to about 6 cm lymphoproliferative process. The injury partially involves the aortic arch and its branches, displaces the trachea to the right, and contacts the esophagus. After 8 days, she was discharged from the hospital.

After 13 days of hospital discharge, she returned to the hospital due to spontaneous ventilation damage, with lower airway critical obstruction due to mediastinal lymphadenopathy, being immediately placed on mechanical ventilation (MV) and transferred to the intensive care unit (ICU). Patient underwent percutaneous biopsy and immunohistochemistry of the mediastinal mass, indicating LNHDGCB with a high degree of cell proliferation. Emergency radiotherapy treatment directed to the mediastinal mass due to lymphoma was started and chemotherapy treatment previously started for metastatic lung cancer was resumed. During the second hospitalization, the patient presented non-oliguric AKI without criteria of tumor lysis and febrile neutropenia, in addition to pulmonary sepsis evidenced by blood culture with the presence of *coagulase negative Staphylococcus* and *Klebsiella pneumoniae* resistant to carbapenems. Then, the patient was discharged from the ICU after 23 days of hospitalization and was

transferred to the infirmary. In the ward, the patient had nausea, vomiting, severe oropharyngeal dysphagia, and onset of secondary AKI. Chest and abdomen CT scans were performed to follow-up chemotherapy and radiotherapy, which showed a reduction in periaortic retroperitoneal lymph node enlargement, making the oncology team consider the patient's lymphoma as curable. Thus, she was discharged from radiotherapy and hospital after 48 days of hospitalization, with the indication for follow-up chemotherapy due to lymphoma and metastatic lung cancer.

Ten days after discharge, she returned to the hospital with complaints of diffuse abdominal pain, vomiting, and constipation. Upon arrival, on physical examination, she had febrile neutropenia, hyperglycemia, hypotension, tachycardia, and anuria, besides secondary pancytopenia due to chemotherapy. Laboratory tests showed acute loss of renal function and respiratory focus sepsis. These findings, in addition to immunosuppression by radiotherapy and chemotherapy, suggested death risk. The patient was admitted to the ICU again and needed MV. Eight days after her rehospitalization—in the third consecutive hospitalization, a significant worsening of the ventilatory pattern of multifactorial cause was noted in a patient with proliferative disease already fully supported within the established therapeutic proposals, causing the medical team to start exclusive palliative care and use of morphine. The patient died on the same day. During her three hospitalizations, the patient received corticosteroids, insulin, vasoactive drugs, diuretics, laxatives, empirical treatments for tracheobronchitis, Filgrastima[®], Meropenem[®], morphine, unfractionated heparin and Vancomycin[®].

3. Discussion

The patient in the present report was diagnosed with LNHDGCB. LNHDGCB is an NHL with a high degree of cell proliferation that has a prevalence of 30% among all lymphomas [1]. Risk factors for its development involve age, sex, and ethnicity, being more common in middle-aged or elderly white men [1]. The patient in this report was of black ethnicity and was 59 years old, opposite characteristics to the disease risk factors. Considering patients with NHL, 66% have lymphadenopathy, 40% have fever associated with night sweats and weight loss and 20% have mediastinal mass [2]. In addition, muscle atrophy and spontaneous pain, including progressive dysphagia with choking, severe oropharyngeal dysphagia and diffuse abdominal pain are common [3] [4] [5]. In relation to LNHDGCB, enlarged lymph nodes, anemia, and bone pain are the main symptoms [18]. The patient came to the hospital because of these symptoms, and, except for the characteristics related to the risk factors, was a classic case of LNHDGCB. After the initial diagnosis, the medical team recommended radiotherapy and resumed chemotherapy for previous metastatic lung cancer with tumor necrosis.

Lung cancer has as main symptoms cough, chest pain, pain in the arm or shoulder, dyspnea, and weight loss [7]. The patient in the present report had

these symptoms and had bone metastasis associated with lung cancer, indicating that lung cancer had progressed systemically [8]. Risk factors associated with lung cancer include smoking, socioeconomic profile and low education. Thus, improved survival is related to changes in lifestyle, such as smoking cessation [19]. In this report, the patient was a smoker, and this habit, as well as being a risk factor and worsening the survival of patients with lung cancer, can cause tumor necrosis due to the PD-L1/PD-1 interaction, which can suppress the response of T cells and cause cell death [20]. Tumor necrosis can also be caused by osmotic rupture of lung cells on account of chemotherapy [21]. In addition, chemotherapy is a very aggressive treatment that can cause side effects, such as nausea and vomiting [5]. Constipation can also appear owing to the low water intake of patients during treatment [5]. Besides these comorbidities, the patient presented pulmonary sepsis, AKI, and febrile neutropenia during her hospitalizations.

The set of severe manifestations throughout the body produced by an infection characterizes sepsis, and cancer patients are the most affected by this condition [12]. Sepsis lowers blood pressure, causing a reduction in the glomerular filtration rate and consequently AKI [4]. Thus, the main cause of AKI in critically ill patients is sepsis [16]. However, AKI can also happen due to the nephrotoxicity of chemotherapeutic agents, since the kidneys are the main route of elimination of antineoplastics and metabolites [15]. Moreover, AKI can occur because of hydroelectrolytic complications associated with NHL, such as hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia [14]. AKI worsens the prognosis of any associated comorbidity as it increases the mortality rate in patients with cancer [22], causes complications in ICU patients with sepsis [16] and increases the cytotoxic effects of chemotherapy [23]. One of the most common complications of chemotherapy is febrile neutropenia, which is often associated with anemia and thrombocytopenia [24]. The cytotoxic effects and the suppression of neutrophil production caused by chemotherapy decrease the signs and symptoms of infection response, so that fever may be the only indication. Despite the apparent lack of clinical symptoms of infection, febrile neutropenia must be treated urgently due to the imminent risk of rapid spread of the infection, which can lead to death [17].

This report presents a case of a patient with LNHDGCB and lung cancer with metastasis and tumor necrosis who presented sepsis, AKI, and febrile neutropenia during three consecutive hospitalizations. The patient died due to complications of her comorbidities and significant worsening of her ventilatory pattern of a multifactorial cause. Something unusual in the literature related to this case is the risk factors for LNHDGCB, such as age, sex, and ethnicity. LNHDGCB is more common in middle-aged or elderly white men [1], while the patient reported here was black and was 59 years old. The evaluation of risk factors in the follow-up of a clinical case is important and must be considered. However, they are not absolute determinants and may occur in patients who do not confirm the

list of risk factors. In this sense, the present study offers this contribution to colleagues.

4. Conclusion

The present report presented a case of a patient with LNHDGCB associated with metastatic lung cancer and multifactorial complications. As we have seen, the patient had mostly classic characteristics of her comorbidities. However, the overlapping of interrelated comorbidities led to the outcome of death. The literature shows that female smokers are at high risk of developing NHL associated with lung cancer [21], that NHL patients with febrile neutropenia are more likely to develop AKI [14], and that sepsis is the main cause of AKI in patients seriously ill [16], complications presented by the reported patient. However, it can be highlighted that something unusual in the literature presented in this case report is the risk factors for LNHDGCB, such as age, sex, and ethnicity, since this type of lymphoma is more common in middle-aged or elderly white men [1], opposing the risk factors described in this case.

Acknowledgements

This study was funded in part by the Coordination of Improvement of Higher Level Personnel—Brazil (CAPES), Finance Code 001 and by the Research Foundation of the State of Rio Grande do Sul (FAPERGS).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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