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Metachronous or Synchronous Presentation of Acute Myeloid Leukemia and Lung Cancer: A Single-Center Experience

Akut Miyeloid Lösemi ve Akciğer Kanserinin Metakron veya Senkron Görülmesi: Tek Merkez Deneyimi

ABSTRACT

Objective:

Acute myeloid leukemia (AML) is the most common type of leukemia in adults. Lung cancer is one of the most common types of cancer. The concomitant presentation of AML and lung cancer is extremely rare. This study aimed to report a case series of concomitant presentation of acute myeloid leukemia and lung cancer as metachronous or synchronous.

Material and Methods:

We describe six cases with diagnosis of these two diseases in between the years of 2016-2020 in our hospital. Patients treated in our hospital were retrospectively reviewed. Clinical characteristics, immunohistochemical and genetic findings, treatments and outcomes were collected.

Results:

All six cases that made up our series had a smoking history. Case two had radiotherapy, and it was cranial radiotherapy for prophylaxis. Radiotherapy was also given to case three for lung cancer. The other cases had no history of radiotherapy before the diagnosis of AML. We detected lung cancer as metachronous in cases two, three, four and five; and synchronously in cases one and six.

Conclusion:

Coexistence of AML and lung cancer is extremely rare. However, it should be kept in mind that we may encounter these two malignancies in a patient at the same time.

Key Words:

Acute myeloid leukemia, Lung cancer, Metachronous, Synchronous

ÖZ

Amaç:

Akut miyeloid lösemi (AML), yetişkinlerde en sık karşılaşılan akut lösemi tipidir. Akciğer kanseri, en yaygın kanser türlerinden biridir. Eşzamanlı AML ve akciğer kanserinin ortaya çıkışı oldukça nadirdir. Bu çalışma, AML ve akciğer kanserinin metakron veya senkron olarak görüldüğü bir vaka serisini tanımlamaktadır.

Gereç ve Yöntemler:

2016-2020 yılları arasında hastanemizde tedavi gören hastalar geriye dönük olarak incelendi. AML ve akciğer kanserinin metakron veya senkron olarak görüldüğü toplam altı olgu tespit edildi. Hastaların klinik özellikleri, immünohistokimyasal, genetik bulgular, verilen tedavi rejimleri retrospektif olarak incelendi.

Bulgular:

Tespit edilen altı olgunun hepsinde sigara öyküsü vardı. İkinci olguda profilaksi için kranial radyoterapi uygulanmıştı. Üçüncü olguda da akciğer kanseri için radyoterapi uygulanmıştı. Diğer olgularda AML tanısı konmadan önce radyoterapi öyküsü yoktu. Akciğer kanseri iki, üç, dört ve beşinci olguda metakron olarak ve bir ve altıncı olguda senkron olarak tespit edildi.

Sonuç:

AML ve akciğer kanserinin bir arada bulunması oldukça nadirdir. Ancak, aynı hastada bu iki maligniteyle karşılaşabileceğimiz de unutulmamalıdır.

Anahtar Kelimeler:

Akut miyeloid lösemi, Akciğer kanseri, Metakron, Senkron

INTRODUCTION

According to the World Health Organization (WHO) data, 18.1 million new cancer cases and 9.6 million cancer-related deaths were reported in 2018. Despite recent advances in both etiology and treatment, it is both scary and sad that the global picture is this way. Among the top cancer types in the ranking are lung cancer, breast cancer, and colorectal cancer. Lung cancer maintains its importance as first cancer in the ranking of causes of death (1.8 million deaths, 18.4% of total). One of the most important reasons for this is the poor prognosis of this cancer (1).

Acute myeloid leukemia (AML) is the most common type of leukemia seen in adults. AML accounts for approximately 80% of adult leukemias. The prognosis is poor, especially in advanced age. Despite the new treatment options, 70% of AML patients are older than 65 and die within the first year after diagnosis. Most patients with AML are healthy individuals before the disease, and AML develops de novo in these people. However, sometimes it may develop in patients with another underlying hematological disease or secondary to previous treatments. The main treatment agents emphasized are topoisomerase II inhibitors, alkylating agents, or radiation (2). Treatment-associated AML (t-AML) is mainly seen in patients with hematological malignancy and breast cancer patients (3, 4).

Although lung cancer and acute myeloid leukemia appear to be two very different malignancies, recently, case reports have been reported that they can be encountered in the same patient as metachronous or synchronous. According to the Moertel definition, the newly formed cancer type within 6 months after the diagnosis of primary cancer can be called synchronous, and cancers develop longer than 6 months as metachronous (5 ,6).

We aimed to report a case series of concomitant presentations of acute myeloid leukemia and lung cancer as metachronous or synchronous.

MATERIAL and METHODS

We wanted to share information about six cases diagnosed with these two diseases between the years 2016-2020. Patients treated in our hospital from 2016 to 2020 were retrospectively reviewed. Clinical characteristics, immunohistochemical and genetic findings, treatments, and outcomes were collected. This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Pamukkale Medical Faculty Ethical Committee, Pamukkale University (approval number: 07.07.2020/13). All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

RESULTS

The characteristics of 6 patients are reviewed below:

Case 1:

The 86-year-old male patient was diagnosed with synchronous AML and non-small cell lung carcinoma. The patient also had a smoking history (70 packs/year).

History of AML: The patient's diagnosis was classified as AML M7 according to the FAB classification. Fluorescence in situ hybridization (FISH) showed trisomy 8 positivity. He received six cycles of 5-Azacitidine. He was in remission, and after that, he received three more cycles of 5-Azacitidine. Venetoclax was started in February 2020 for the patient who subsequently relapsed. About 16 months later after diagnosis, he died due to pneumonia and pleural effusion.

History of Lung Cancer: The patient diagnosed with synchronous, clinical-stage 2A squamous cell lung carcinoma could not be given chemotherapy due to thrombocytopenia. Radiotherapy was planned for palliative purposes when the platelets reached above 50,000/uL. However, it could not be administered when thrombocytopenia did not improve.

Case 2:

The 57-year-old male patient was diagnosed with small cell lung carcinoma. He was diagnosed with AML at the age of 60. The patient also had a smoking history (80 packs /year).

History of Lung Cancer: The patient was was diagnosed with limited-stage small cell lung carcinoma his treatment started with concurrent radiotherapy with cisplatin. Subsequently, three cycles of cisplatin and etoposide were given. Upon receiving treatment response, he received cranial radiotherapy for prophylaxis and oral etoposide maintenance treatment. Approximately 3 years later, AML was diagnosed by bone marrow biopsy performed for pancytopenia.

History of AML: The patient's diagnosis was classified as AML M5. He received 5 + 2 remission induction therapy. The patient then received three cycles of consolidation therapy. About 6 months after the diagnosis of AML, he died due to relapse, fever, and pneumonia.

Case 3:

The 53-year-old male patient who was diagnosed with lung adenocarcinoma was diagnosed with AML 6 years later. The patient had a smoking history of 30 packs/year.

History of Lung Cancer: After the diagnosis of lung adenocarcinoma, left lung upper lobe wedge resection was done. After that, adjuvant chemotherapy (cisplatin + gemcitabine) and radiotherapy were applied. Erlotinib was initiated due to the progressive lymph node under gemcitabine treatment. The patient underwent right lung upper lobe wedge resection because of the single focal metastasis, 2 years after the diagnosis. Then he received adjuvant cisplatin and vinorelbine treatment. The patient with progression received two cycles of docetaxel, followed by six cycles of paclitaxel and carboplatin. The patient, whose chemotherapy tolerance decreased and the stable response was achieved, was maintained with oral etoposide treatment. Approximately 2 years after oral etoposide treatment, the patient was diagnosed with AML.

History of AML: It has been interpreted as AML M5 according to the FAB classification. Structural anomalies of which origin could not be determined were observed in chromosomes 7 and 10. Also, 17p deletion and a translocation including the 21st chromosome were identified by FISH. After 7 + 3 treatment, reinduction treatment was given due to insufficient response. After the second consolidation, 5-Azacitidine was started due to recurrence and neurological side effects of cytarabine. After four cycles of 5-azacitidine, relapse developed. FISH showed an increase in the number of copies of the MLL gene. At last, decitabine treatment was started. After one course of decitabine treatment and 16 months after diagnosis of AML, the patient died because of refractory disease, leucostasis findings of the lung, and pneumonia.

Case 4:

At the age of 64, the patient was diagnosed with lung cancer. He had a smoking history of 50 packs/year. He also had polycythemia vera before the diagnosis of AML. At the age of 70, he was diagnosed with AML.

History of Lung Cancer: The patient, who underwent left upper lobectomy in December 2013, was diagnosed with Stage 1A lung adenocarcinoma. The medical oncology department followed up the early-stage patient without any other treatment.

History of AML: Six years had passed after the lung cancer diagnosis when the patient was classified as AML M2. FISH identified 5q and 17p deletion. He received three cycles of consolidation therapy after 5 + 2 induction therapy with the diagnosis of AML M2. Recurrence developed while being followed up with remission. He received three cycles of 5-azacitidine treatment. Eleven months after diagnosis of AML, he died due to pneumonia.

Case 5:

At the age of 63, the patient was diagnosed with MDS RAEB2 (2013). At the age of 64, he was diagnosed with lung cancer. The patient had a smoking history of 95 packs/year. There is also a history of comorbidity with colon cancer (2017). He was diagnosed with AML in 2018.

History of Lung Cancer: The patient, who was examined for hemoptysis, was diagnosed with invasive mucinous carcinoma with enteric morphology due to right upper lobectomy in 2014. Follow-up was taken after adjuvant four cycles of paclitaxel and carboplatin treatment. During the follow-up, she was operated upon detection of colon adenocarcinoma. She received six cycles of adjuvant capecitabine + oxaliplatin treatment. In the follow-up in 2018, the patient was diagnosed with AML.

History of AML: The patient was evaluated as AML M2. The conventional and molecular cytogenetics as FISH was regular. After 7 + 3 induction therapy, three consolidation treatments were given. After 2 months, the recurrence of the disease developed. 5-Azacitidine was started. After six cycles of 5- Azacytidine, recurrence developed. The combination therapy protocol as venetoclax and decitabine is planned. The follow-up of the patient is continuing.

Case 6:

A 73-year-old male patient was diagnosed with synchronous AML and non-small cell lung carcinoma. There was a smoking history of 45 packs/year. In February 2017, he was diagnosed with AML.

History of AML: The patient was classified as AML M2. A normal karyotype was found by cytogenetics. After 7 +3 induction (containing mitoxantrone and cytarabine) and one course of consolidation, he was in the remission phase.

History of Lung Cancer: In April 2017, a mass involving the bronchus in the upper lobe of the left lung was detected in the patient examined for hemoptysis. The biopsy was diagnosed with squamous cell lung carcinoma. Since he refused the operation, he received palliative radiotherapy for hemoptysis, and then four cycles of cisplatin + gemcitabine chemotherapy were given. The patient died due to pneumonia, 9 months after diagnosis of lung cancer.

DISCUSSION

In recent years, new developments in treatment (targeted agents and immunotherapy) have positively affected the prognosis of lung cancer. As the survival time increases, the risk and frequency of other diseases, malignancies, and AML increase in these patients. Smoking has an essential place in the etiology of lung cancer and AML. It has long been known that smoking causes lung cancer. However, it is accepted by WHO in 2004 that smoking causes AML (7). All six cases that made up our series had a smoking history.

Smoking may constitute an etiological reason for our patients. Another common etiological reason for AML and lung cancer is exposure to ionizing radiation (8, 9). In addition, it is also stated that the frequency of acute myeloid leukemia increases in lung cancer patients who received radiotherapy (10). Similarly, it has been reported that the risk of lung cancer increases in patients who received radiotherapy due to another malignancy (such as breast cancer, Hodgkin lymphoma) (11, 12). Second case had radiotherapy, and it was cranial radiotherapy for prophylaxis. Radiotherapy was also given to third case for lung cancer. The other cases had no history of radiotherapy before the diagnosis of AML.

Natori K et al. reported four cases of lung cancer and AML of the metachronous type. He reported two of these patients as treatment-associated AML (t-AML) (13). Sampath KJ et al., reported a synchronous AML and lung cancer case (14). We detected lung cancer as metachronous in cases two, three, four and five; and synchronously in cases one and six.

There is a unique title in the WHO 2016 classification of myeloid neoplasms and acute myeloid leukemia as "treatment-associated Myeloid Neoplasm" (t-MNs). Treatment-Related Myeloid Neoplasms have been defined as myeloid neoplasms that develop following cytotoxic therapy. Treatment-Related Myeloid Neoplasms have been defined as myeloid neoplasms that develop following cytotoxic therapy. t-MNs can be divided into treatment-related MDS (t-MDS) or AML (t-AML). While making the final diagnosis of the disease, the associated cytogenetic disorder should also be considered for treatment and prognosis prediction. It has been shown that some of these patients have germline mutations in cancer-sensitive genes (15).

In recent years, it is thought that t-AML can be seen in two ways depending on the drugs causing and molecular cytogenetic related clinical features: 1-) Topoisomerase II inhibitor-associated t-AML 2-) t-AML due to radiotherapy or alkylating agents. Topoisomerase II inhibitor-associated t-AML is often expected to occur within 1-3 years after treatment. It has been shown that the incidence increases from 0.5% to 2.6% when the total dose of topoisomerase is 2000 mg/m2 or more. Mostly 11q23 and 21q22 chromosomal abnormalities are observed in t-AML associated with topoisomerase II inhibitor (16). On the other hand, t-AML due to alkylating agents and radiotherapy usually develops 5-7 years after treatment, and patients are mostly seen with monosomy (16, 17). In our series, as shown in table I, third case's chemotherapeutics included cisplatin, gemcitabine, erlotinib, vinorelbine, docetaxel, paclitaxel, carboplatin and etoposide. In that case (third case), structural anomalies of which origin could not be determined in chromosomes 7 and 10; also, 17p deletion and a translocation including 21st chromosome were identified by FISH.

Table I. Total drug doses of patients due to lung cancer

Case		Total Dose (mg):
1	-	-
2	Cisplatin	1020
	Etoposide	28725
3	Cisplatin	1300
	Gemcitabine	19800
	Vinorelbine	600
	Docetaxel	280
	Paclitaxel	1950
	Carboplatin	3300
	Etoposide	-*
4	-	-
5	Paclitaxel	1800
	Carboplatin	1400
	Oxaliplatin	840
6	Gemcitabine	15200
	Cisplatin	400

* It is not calculated because of irregular usage of patient.

CONCLUSION

One should be alert for developing other malignancies during the follow-up of patients with prolonged survival with the advances in lung carcinoma treatment. It should be kept in mind that MDS and AML may be among these malignancies.

Ethics Committee Approval:
This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Pamukkale Medical Faculty Ethical Committee, Pamukkale University (approval number: 07.07.2020/13).

Informed Consent:
All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Author Contributions:
Concept – B.Ü.K., A.G.D.; Design- B.Ü.K., A.G.D.; Supervision – B.Ü.K., N.G.; Resources - B.Ü.K., A.G.D.,T.D.,G.A.Ç.,S.H., F.B.; Materials - B.Ü.K., A.G.D.,T.D.,G.A.Ç.,S.H., F.B.; Data Collection and/or Processing - B.Ü.K., A.G.D.,T.D.,G.A.Ç.,S.H., F.B.; Analysis and/ or Interpretation - B.Ü.K., Y.A.K., A.G.D.; Literature Search - B.Ü.K., A.G.D.; Writing Manuscript - B.Ü.K., A.G.D.; Critical Review - B.Ü.K., N.G., A.G.D.

Conflict of Interest:
The authors have no conflict of interest to declare.

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