Development of second primary multiple myeloma five years after treatment for limited-stage small cell lung cancer: a rare case report

ABSTRACT

Introduction. The development of a second primary malignancy (SPM) following small cell lung cancer (SCLC) has been previously reported in the literature. Especially smoking-related malignancy coupling is well known. The development of multiple myeloma (MM) in long-term survivors after treatment for SCLC is unknown. Here, we report the first case in the literature who developed MM 5 years after treatment for limited-stage SCLC.

Case report. A 67-year-old male patient was diagnosed with limited-stage SCLC. After he received chemotherapy and radiotherapy, he was followed up without medication. He was admitted to the hospital with back pain and dyspnea 5 years after the diagnosis of small cell lung cancer. MRI revealed osteolytic lesions in the vertebrae. Laboratory testing revealed a markedly elevated serum IgA and an elevated serum beta-2 microglobulin level. Serum immunofixation revealed IgA lambda-type M-protein. Lambda excretion in urine immunofixation electrophoresis was observed. Bone marrow aspiration revealed the frequency of plasma cells to be 80% of all nucleated cells. Hence, the final diagnosis revealed IgA lambda free light chain MM. Treatment was given for multiple myeloma. In the follow-up, the patient experienced increased dyspnea and developed bilateral pleural effusion. The cytology sent from thoracentesis sampling was reported as plasmocyte-rich material. The patient fell into a coma and died in an intensive care unit.

Conclusion. We presented the development of MM 5 years after treatment in a patient with SCLC who were treated for one year and then followed up with stable findings. It should be kept in mind that a patient with SCLC who is a long-term survivor and presents with back pain may have developed a primary malignancy originating from bone marrow rather than a bone metastasis. Patients should be advised smoking cessation after the treatment and diagnosis of SCLC. Also, the patients with SCLC who are long-term survivors should be closely monitored for the development of SPM.

Key words: small cell lung cancer, multiple myeloma, second primary malignancy
malignancy (SPM) associated with smoking was found to be high in patients with lung cancer. The concomitance of a malignancy originating from plasma cells such as multiple myeloma and SCLC has not been described in the literature. In this case report, we present the development of multiple myeloma following SCLC treatment.

Case presentation

A 67-year-old male patient was diagnosed with limited-stage SCLC in January 2012, proven by thoracic and abdomino-pelvic computed tomography (CT) scan and right supraclavicular lymphadenopathy biopsy. The patient had no history of other medical comorbidities. The patient had a smoking history of 48 pack-years until the moment of diagnosis. He was treated with four cycles of cisplatin + etoposide combination chemotherapy (cisplatin 80 mg/m² intravenous (iv) infusion on D1, etoposide 100 mg/m² iv infusion on D1–3, repeated every 3 weeks) along with concurrent thoracic radiotherapy. In July 2012, he was treated for nine weeks of weekly topotecan (4 mg/m² iv infusion on D1, D8 and D15, repeated every 28 days) followed by six cycles of cyclophosphamide+doxorubicin+vincristin (cyclophosphamide 1000 mg/m² iv infusion on D1, doxorubicin 40 mg/m² iv infusion on D1, vincristine 1 mg/m² iv infusion on D1, repeated every 3 weeks) chemotherapy due to progression of lesions in the lung. After treatment, the lymph nodes in the cervical region disappeared, and the soft tissue mass in the right para-tracheal area was markedly regressed in comparison with previous imaging. With these findings, the patient was monitored without drug treatment. There was no cigarette use during the one year when the patient received chemotherapy. However, he started to smoke again six months after the end of the treatment (one pack of cigarettes a day. In the last follow-up imaging performed in May 2017, the findings of stable disease were persisted. He was admitted to the Medical Oncology Department with back pain and dyspnea in August 2017. He had back pain for about two months and did not respond to painkillers. The physical examination revealed diffuse rhonchus in both lungs. Other vital signs and the physical examination were normal. Laboratory tests performed are displayed in Table 1. Bone marrow biopsy, serum protein electrophoresis and thoracic and lumbar magnetic resonance imaging (MRI) were done to rule out metastatic deposits in the patient and to know the cause of pancytopenia, hypercalcemia and elevated erythrocyte sedimentation rate (ESR). MRI revealed osteolytic lesions in the vertebrae (Fig. 1). Laboratory testing revealed a markedly elevated serum immunoglobulin (Ig) A (IgA) level (59.3 g/L, reference range: 0.7–4 g/L) and an elevated serum beta-2 microglobulin level (5.33 mg/L, reference range: 0.97–2.64 mg/L) (Tab. 2).

Table 1. Serum laboratory levels and protein electrophoresis

| Parameter   | Level     | Normal range |
|-------------|-----------|--------------|
| WBCc        | 3.6 × 10³/uL | (4–10)       |
| Neu         | 1.86 × 10³/uL | (1.5–7.3)   |
| Hb          | 8.5 g/dL   | (12.1–17.2)  |
| Plt         | 97 × 10³/uL | (150–400)    |
| Sedimentation rate | > 140 mm/hour | (0–20)  |
| Ure         | 31 mg/dL   | (15–44)      |
| Cre         | 1.17 mg/dL | (0.72–1.25)  |
| Na          | 142 mmol/L | (136–145)    |
| K           | 4.8 mmol/L | (3.5–5.1)    |
| Ca          | 11.47 mg/dL| (8.4–10.2)   |
| Total protein | 7.8 mmol/L | (3.5–5.1)   |
| Albumin     | 2.2 g/dL   | (3.5–5)      |

The rates of protein electrophoresis

| ALBUMIN | 31.11% | (55.8–65) |
| ALFA1    | 4.37%  | (2.2–4.6) |
| ALFA2    | 8.08%  | (8.2–12.5) |
| BETA     | 22.40% | (7.2–14.2) |
| GAMA     | 34.04% | (11.5–18.6) |

Figure 1. Sagittal magnetic resonance imaging with multiple bone osteolytic lesions of the cervical and thoracic spine

Serum immunofixation revealed IgA lambda-type M-protein. Lambda excretion in urine immunofixation electrophoresis was observed. Bone marrow aspiration revealed the frequency of plasma cells to be 80% of all nucleated cells. Microscopic examination and flow cytometric analysis of bone marrow aspirate revealed...
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hemithorax and regional lymph nodes, median survivals
relapses within months despite treatment. For patients
chemotherapy, and chest irradiation [8, 9]. In a study
ing forty-seven patients who were identified to be free of
non-small cell lung cancer, two with gastric cancer, and
one with prostate cancer) [10]. In another study includ-
ing two years, SPM was observed in seven patients (four with
malignancy developed in these patients was leukemia
[12–15]. However, MM development as SPM in patients
with SCLC has never been reported. To the best of our
knowledge, this is the first reported case in the literature.

Discussion

SCLC is an aggressive form of lung cancer character-
ized by rapid doubling time and high growth rate and
early metastasis development and is strongly associated
with smoking. The most important prognostic factor
in patients with SCLC is the extent of disease (stage)
at presentation. Although SCLC is highly responsive
to both chemotherapy and radiotherapy, it commonly
relapses within months despite treatment. For patients
with the limited-stage disease, limited to the ipsilateral
hemithorax and regional lymph nodes, median survivals
range from 15 to 20 months, and the reported five-year
survival rate is 10 to 13 percent. Patients with the
limited-stage disease are primarily treated with a com-
bination of chemotherapy (cisplatin plus etoposide)
and radiation therapy. SCLC has been rare in never
smokers. Exposure to tobacco and multiple genetic
defects including p53 mutations, loss of the retinoblas-

elevated numbers of CD38-positive abnormal plasma
cells. In the bone marrow FISH analysis, 13q14.3 80%
normal 20% number 13 chromosomal monosomy
signals were observed, 25% CKS1B gene expression
was increased. Also, p53 and Ig heavy chain (IgH)/
breakapart were normal. Hence, the final diagnosis
revealed IgA lambda free light chain MM. The patient
was transferred to the hematology clinic and was treated
with zoledronic acid (4 mg iv infusion) and one cycle of
toxotizomib plus cyclophosphamide plus dexametha-
sone (bortezomib 1.5 mg/m² subcutaneously on D1, 8,
15, 22, cyclophosphamide 300 mg/m² orally on D1, 8,
15, 22, dexamethasone 40 mg orally on D1, 8, 15, 22,
repeated every 28 days) combination chemotherapy.

In the follow-up, the patient experienced increased
dyspnea and developed bilateral pleural effusion. The
cytology sent from thoracentesis sampling was reported
as plasmocyte rich material. The patient was admitted
to the intensive care unit because of severe respiratory
distress. The patient fell into a coma and died on the
3rd day of admission to an intensive care unit.

Discussion

SCLC is an aggressive form of lung cancer character-
ized by rapid doubling time and high growth rate and
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bination of chemotherapy (cisplatin plus etoposide)
and radiation therapy. SCLC has been rare in never
smokers. Exposure to tobacco and multiple genetic
defects including p53 mutations, loss of the retinoblas-
toma gene (RB1) function at 13q14, loss of PTEN,
MYC amplification, activation of telomerase, and strong
expression of cKit are related with oncogenesis in SCLC.
However, mutations in the EGFR and KRAS oncogenes
and p16 abnormalities are rare [3, 4].

MM is characterized by the neoplastic proliferation
of plasma cells producing a monoclonal immunoglobu-
in. Older age, immunosuppression, environmental
exposures such as radiation, benzene, and other organic
solvents including herbicides, and insecticides, and some
primary (IgH chain translocations, trisomies) and sec-
ondary cytogenetic abnormalities (secondary IgH trans-
locations, deletion of 17p13 on p53 locus, Ras mutations,
activation of NF kappa B) appear to play a major role
in the development of MM [5, 6].

Careful monitoring for the development of SPM in
patients with SCLC is necessary for long-term survivors,
because the risk of developing SPM in these patients
is significantly increased. The cessation of cigarette
smoking after successful therapy is associated with
a significantly decreased risk of an SPM [7]. The risk
of SPM was increased by a number of chemotherapy
cycles > 6, an age of > 60, treatment with combination
chemotherapy, and chest irradiation [8, 9]. In a study
including sixty-one patients who survived for more than
two years, SPM was observed in seven patients (four with
non-small cell lung cancer, two with gastric cancer, and
one with prostate cancer) [10]. In another study includ-
ing forty-seven patients who were identified to be free of
disease at two years, SPM was observed in 14 patients. In
these patients, aerodigestive tract malignancies associ-
ated with smoking as SPM has been developed [11].
Also, in previous studies, the development of hemato-
logic malignancy as SPM in long-term survivors after
treatment for SCLC has been reported. Hematologic
malignancy developed in these patients was leukemia
[12–15]. However, MM development as SPM in patients
with SCLC has never been reported. To the best of our
knowledge, this is the first reported case in the literature.
The patient stopped smoking during the treatment for
SCLC, but had started again six months after the end of the
treatment. From the literature and past experience,
we were expecting smoking-induced SPM development,
but we were surprised by the development of MM in our
patient. Because MM is not a smoking-related
malignancy, we think that increased predisposition to
MM development may relate to secondary effects of
multimodality treatment including chemotherapy and
radiotherapy.

Conclusion

We presented the development of MM 5 years after
treatment in a patient with SCLC who was treated for

Table 2. Serum immunoglobulin levels

| Parameter       | Level  | Normal range |
|-----------------|--------|--------------|
| Immunoglobulin G| 1.53 g/L| (7–16)       |
| Immunoglobulin A| 59.3 g/L| (0.7–4)      |
| Immunoglobulin M| 0.186 g/L| (0.4–2.3) |
| Lambda free light chain| 62.2 mg/dL| (8.3–27) |
| Kappa free light chain| 9.29 mg/dL| (6.7–22.4) |
| Free kappa to free lambda ratio| 0.15| (0.26–1,65) |
| Beta 2 microglobulin| 5.33 mg/L| (0.97–2.64) |
one year and then followed up with stable findings. It should be kept in mind that a patient with SCLC who is a long-term survivor and presents with back pain may have developed a primary malignancy originating from bone marrow rather than a bone metastasis. Patients should be advised smoking cessation after the treatment and diagnosis of SCLC. Also, the patients with SCLC who are long-term survivors should be closely monitored for the development of SPM.

**Clinical practice points**

Patients with long-term remission after being treated for small cell lung cancer must be closely followed up for second primary cancers.

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**Conflict of interest**

The authors have declared no conflicts of interest.

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