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Regression of a Primary Pulmonary Adenocarcinoma after Zoledronic Acid Monotherapy

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ABSTRACT

Bisphosphonates are widely used for the treatment of metastatic skeletal tumors and hypercalcemia resulting from malignant tumors. Zoledronic acid (ZOL), a third-generation bisphosphonate agent, was recently demonstrated to show synergistic antitumor activity of ZOL when combined with chemotherapy in lung cancer patients. However, whether ZOL exerts direct antitumor activity on lung cancer remains unclear. Here, we report an atypical case encountered while treating a 57-year-old woman with pulmonary adenocarcinoma and multiple metastases of the liver, left adrenal gland, and bone. The nonskeletal lesions, consisting of the primary lesion and hepatic metastasis, regressed after treatment with ZOL alone. We believe this case demonstrates a possible antitumor effect of ZOL against lung cancer.

Key words: *Lung cancer, Bone metastasis, Zoledronic acid, Anti-tumor effect*

Lung cancer is the leading cause of cancer-related deaths worldwide. Patients with advanced lung cancer and bone metastases often experience a markedly reduced quality of life as a result of skeletal-related events (SREs). Novel third-generation bisphosphonates such as zoledronic acid (ZOL) are often used to reduce SREs by inhibiting osteoclast-mediated bone resorption [14]. In addition, recent studies have shown that ZOL possesses antitumor activity, inhibiting cell proliferation, angiogenesis, cell invasion, and cell adhesion [1,2,7-10]. With the exception of lung cancer, there have been few reports of nonskeletal lesions responding to ZOL monotherapy [11,12]. Here, we present an atypical case in which the primary lung cancer regressed after treatment with ZOL alone.

CASE REPORT

A 57-year-old woman was admitted to our hospital with a 2-month history of neck lymphadenopathy and right leg pain. Chest radiography and chest-abdominal computed tomography (CT) examination revealed a tumor (1.6 cm × 1.4 cm) in the right upper pulmonary lobe (Fig. A), multiple small nodular shadows in bilateral lungs, mediastinal lymphadenopathy, space occupying lesion (SOL; 1.5 cm × 1.2 cm; Fig. B) in the liver, and an enlarged left adrenal gland. ^{18}F-fluoro-2-deoxyglucose-positron emission tomography showed multiple metastatic lesions in areas such as the spine, right ilium, and right femur. Laboratory data demonstrated elevated serum carcinoembryonic antigen (CEA) and CYFRA 21-1 levels (16.8 ng/ml and 3.5 ng/ml, respectively). A bronchofiberscopic examination was performed, and adenocarcinoma cells were detected with right B2 washing cytology. However, no epidermal growth factor receptor mutations were identified in the cytological specimens obtained from the primary lesion. Finally, the patient was diagnosed as having pulmonary adenocarcinoma, stage IV (cT1N3M1).

To relieve bone pain, the patient was initially treated with ZOL (4 mg intravenous infusion over 15 min). Palliative irradiation of the neck (C4-Th1) was subsequently performed. Though serum CEA and CYFRA 21-1 levels were stable, right leg pain was slightly reduced after treatment with ZOL. Twenty days after the administration of ZOL, a second CT examination unexpectedly revealed that the size of the primary tumor and hepatic SOL had both decreased (1.2 cm × 1.0 cm and 1.4 cm × 1.1 cm, respectively; Fig. C, D). Thereafter, the patient received carboplatin and paclitaxel as first-line chemotherapy. However, her response to chemotherapy was poor and her general condition gradu-

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ally worsened. She died 7 months later.

DISCUSSION

Bone metastases occur in 30-40% of patients with advanced lung cancer[13] and can lead to various complications including bone pain, pathologic fracture, and spinal cord compression. ZOL is one of the newer bisphosphonate agents and acts as an effective inhibitor of osteoclast-mediated bone resorption. ZOL effectively reduces SREs in patients with multiple myeloma, bone metastases secondary to solid tumors including lung cancer, and hypercalcemia arising from malignancy[6].

The reduction in SREs induced by ZOL is further enhanced when it is used in combination with chemotherapy[5]. Rosen et al[14] reported that in a phase III study for solid carcinoma patients with bone metastasis including lung cancer patients, the ZOL-treated group exhibited fewer SREs than the placebo group.

In vivo and *in vitro* studies have suggested that the antitumor effect of ZOL is derived from its ability to induce apoptosis and inhibit cell growth[8-10]. Furthermore, tumoristatic and angiostatic properties of ZOL, by inhibiting angiogenesis, have been also reported[1,2,7]. Considering the pharmacokinetic features of ZOL, direct activity against tumors is not expected[7]. However, Märten et al reported that administration of ZOL at a pharmacological dosage inhibited proliferation and induced apoptosis in pancreatic carcinoma cells[8]. Recently, Miwa et al reported a case with bone, lung, pleural, and liver metastases from renal cell carcinoma that responded remarkably well to ZOL monotherapy[11]. Furthermore, Gnant et al reported that combined treatment with ZOL and adjuvant endocrine therapy improved the disease-free survival period in premenopausal patients with estrogen-responsive early breast cancer[3]. These reports and the present case suggest that ZOL has anti-tumor properties and might exert a direct anti-tumor effect.

In the present case, it is also possible that the cancer underwent spontaneous remission. Spontaneous remission of cancer is defined as the partial or complete regression of a malignant disease without any medical treatment. The mechanisms responsible for such remission are thought to involve immunological and/or hormonal events,

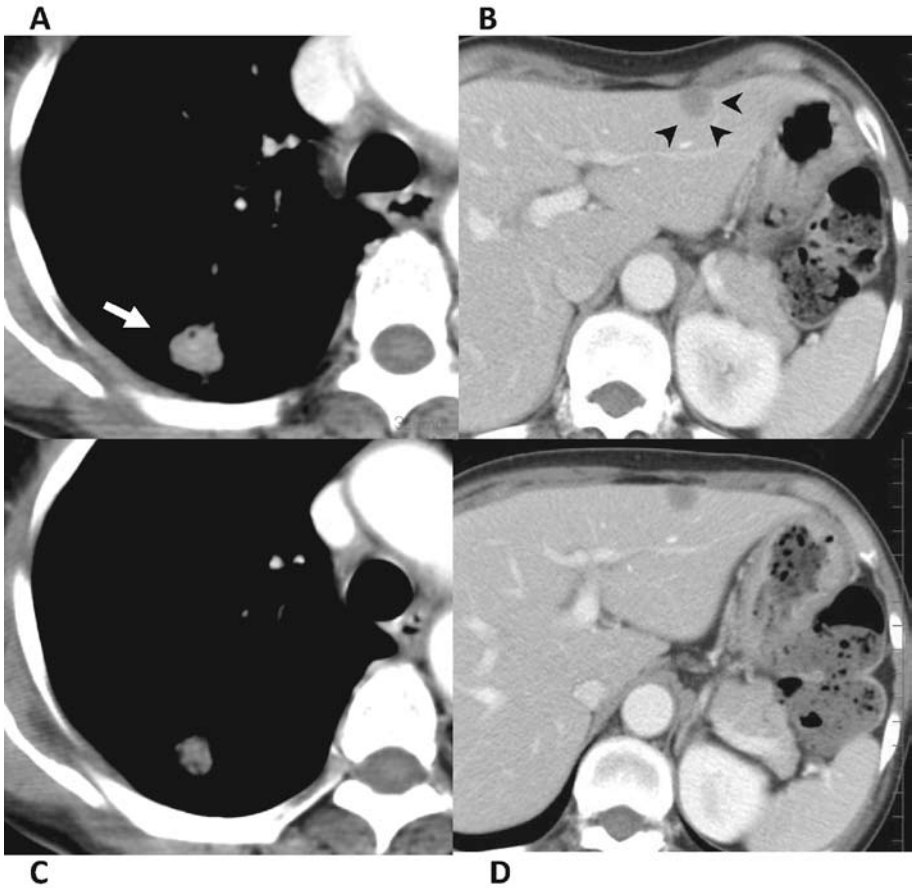

Fig. Lung/abdominal CT results obtained before (A and B) and after (C and D) ZOL therapy.
A: a tumor (1.6 cm × 1.4 cm; arrow) in the right upper pulmonary lobe. B: a SOL (1.5 cm × 1.2 cm; arrowhead) in the liver. C and D: 20 days after administration of ZOL, the primary tumor and hepatic lesion had both decreased in size (1.2 cm × 1.0 cm and 1.4 cm × 1.1 cm, respectively).

although the details are unclear as yet. Invasive events, such as bronchofiberscopic examination or surgery, sometimes enhance the spontaneous remission of cancer. Some reports of spontaneous remission of lung cancer, particularly small-cell lung cancer, have been published. However, such events are much rarer than the spontaneous remission of other solid tumors[4].

In conclusion, we have experienced a rare case in which a primary lung tumor and hepatic metastases responded after treatment with ZOL without chemotherapy. These findings indicate that ZOL might possess a potential antitumor-effect against lung cancer.

Conflict of interest statement

None declared.

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