

Three Young Osteosarcoma Patients with Small Adenocarcinoma or Atypical Adenomatous Hyperplasia of the Lung

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Three young osteosarcoma patients with adenocarcinoma (AD) or atypical adenomatous hyperplasia (AAH) of the lung are reported. A 14-year-old male patient with femoral osteosarcoma had solitary AD (case 1); a 23-year-old female patient with femoral osteosarcoma had AAH and lung metastasis (case 2); and a 17-year-old male patient with humeral osteosarcoma had AD and lung metastasis of osteosarcoma (case 3). They have been the youngest patients with lung cancer or AAH in our hospital. The maximum diameter of each lung tumor on computed tomography (CT) was 0.5, 0.6, and 0.5 cm, respectively. On immunohistochemical analyses, the p53 was positive in both AD and osteosarcoma and negative in both AAH and osteosarcoma. On genomic analyses, p53 mutation was detected in only one osteosarcoma (case 3). Epidermal growth factor receptor (EGFR) mutations, short in-frame deletion in exon 19, and insertion in exon 20 were found in AD, but not in AAH or osteosarcoma. There was no apparent genomic relationship between AD/AAH and osteosarcoma in the young patients in this study. Advances in CT and its applications to osteosarcoma patients as a method of assessing lung metastasis might contribute in large part to the detection of AD/AAH in patients younger than 30. (Ann Thorac Cardiovasc Surg 2010; 16: 358–361)

Key words: lung cancer, young patient, osteosarcoma, computed tomography

Introduction

Lung cancer in a young patient is very rare. Among 13,121 cases of lung cancer treated surgically in Japan in 1999, only 23 patients (0.2%) were less than 30 years old.¹⁾ In our hospital, 3 patients under 30, none of whom had ever smoked, with lung cancer or atypical adenomatous hyperplasia (AAH) had osteosarcoma. All of their tumors were found before the initiation of chemotherapy for

osteosarcoma. These facts suggest the relationship between lung cancer, especially adenocarcinoma (AD) and AAH, and osteosarcoma. We report 3 cases of AD/AAH combined with osteosarcoma. Immunohistochemical and genomic analyses for AD/AAH and the osteosarcoma are also provided.

Case Report

Case 1

A 14-year-old male patient underwent amputation of the left femur for osteosarcoma in July 1997. Preoperative chest computed tomography (CT) revealed a 0.5-cm diameter nodule in the superior segment of the lower lobe of the left lung. No changes in size or features of the nodule were observed on CT after perioperative chemotherapy for osteosarcoma. In November 1997, a thoroscopic wedge resection of the tumor was performed. The tumor was diagnosed histopathologically to be AD. This case

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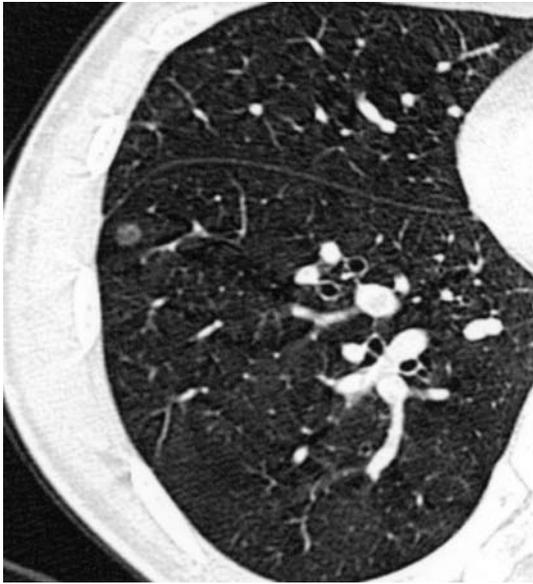


Fig. 1. Chest computed tomography showed small ground-glass opacity in the anterobasal segment of the lower lobe of the right lung (Case 2).

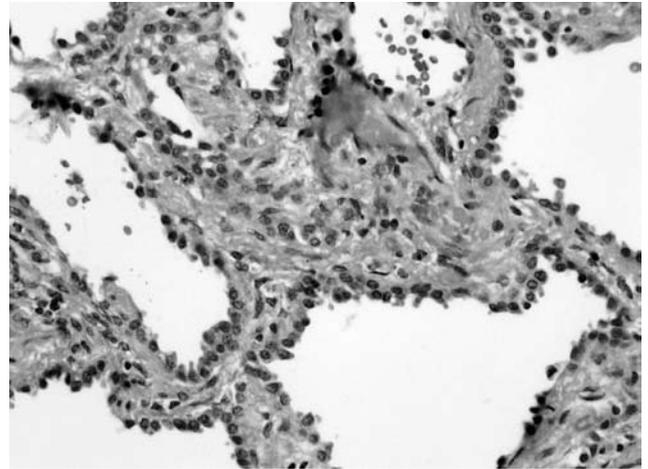


Fig. 2. Microscopic findings of the lung tumor. The monotonous tumor cells were lining intermittently according to the thickened alveolar septa (Case 2).

had been reported previously.²⁾ The patient died in October 2000 of respiratory failure because of multiple lung metastases from osteosarcoma.

Case 2

A 23-year-old female patient underwent artificial knee joint replacement following wide resection of the right femur for osteosarcoma in January 2006. Preoperative CT revealed a 0.6-cm diameter ground-glass opacity (GGO) in the anterobasal segment of the lower lobe of the right lung (Fig. 1). No changes in size or features of the nodule were observed on CT after perioperative chemotherapy for osteosarcoma. In February 2006, a thoracoscopic wedge resection of the tumor was performed. The tumor was diagnosed histopathologically to be AAH (Fig. 2). A follow-up CT in May 2007 revealed a 1.2-cm diameter nodule with a cavity in the superior segment of the lower lobe of the right lung. In June 2007, a thoracoscopic wedge resection of the tumor was performed, and it was histopathologically proved to be metastasis of osteosarcoma. The patient has been alive without disease for 23 months since the metastasectomy.

Case 3

A 17-year-old male patient underwent artificial shoulder joint replacement following wide resection of the left humerus for osteosarcoma after preoperative chemotherapy

in June 2007. Postoperative chest CT revealed a 0.5-cm diameter nodule in the laterobasal segment of the lower lobe of the right lung, and a 0.5-cm diameter GGO in the posterobasal segment of the lower lobe of the right lung (Fig. 3). Retrospective review confirmed that the appearance of the GGO in the posterolateral segment was unchanged compared with that observed on the CT in March 2007. In February 2008, a thoracoscopic wedge resection of the tumors was performed. The tumor in the laterobasal segment was histopathologically proved to be metastasis of osteosarcoma. The other tumor, located at the posterobasal segment, was diagnosed to be bronchioloalveolar carcinoma (BAC) (Fig. 4). The patient has been alive without disease for 15 months since the lung resection.

The study protocol for immunohistochemical and genomic analyses of osteosarcoma and lung tumor specimens was approved by the Ethical Committee of Kumamoto University Hospital in June 2008. After written informed consents from the patients and/or their families had been obtained, immunohistochemistry of p53 and genomic analyses of p53, epidermal growth factor receptor (EGFR) mutations, K-ras, and human epidermal growth factor receptor 2 (HER-2) were performed. The immunohistochemical and genomic analyses were both performed by SRL Laboratory Inc., Tokyo, Japan.

For immunohistochemical analysis of p53 protein in the tumor tissue, deparaffinized 4- μ m-thick sections were examined. A specific mouse anti-p53 protein antibody (Novocastra Laboratories, Newcastle upon Tyne, UK)

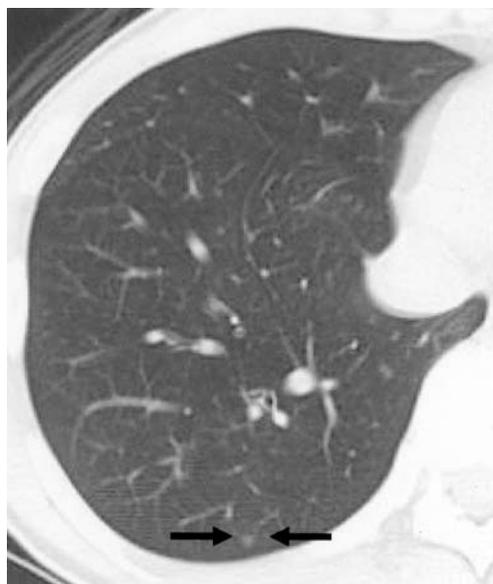


Fig. 3. Chest computed tomography showed small ground-glass opacity in the posterobasal segment of the lower lobe of the right lung (Case 3).

was used for this study.

For genomic analyses of the tumor tissue, DNA was extracted from formalin-fixed, paraffin-embedded specimens. (1) For a detection of EGFR mutation, direct sequencing from EGFR exon 18–21 was performed. (2) For a detection of p53 mutation, a nonradioactive polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis was used to analyze exons 5–8 of the p53 gene for sequence alterations. (3) For K-ras mutation, the nested PCR amplification for exon 2 was performed. (4) For HER-2 mutation, a fluorescence in situ hybridization (FISH) analysis was performed using the PathVysion HER-2 DNA Probe Kit (Vysis, Stuttgart, Germany). Hybridization was performed using hybridization solution containing direct-labeled DNA probes complementary to HER-2 and chromosome 17 centromere. HER-2 and chromosome 17 centromere signals were counted for 60 nuclei per tumor specimen. Overlapping nuclei were excluded from analysis. HER-2 gene amplification was defined as HER-2: chromosome 17 centromere ratio of 2.0 using the Vysis probe. The characteristics of immunohistochemical and genomic analyses for these cases are shown in Table 1.

On immunohistochemical analysis, p53 was positive in both AD and osteosarcoma in Cases 1 and 3, but negative in both AAH and osteosarcoma in Case 2. EGFR mutations, short in-frame deletion in exon 19 (Case 1), and

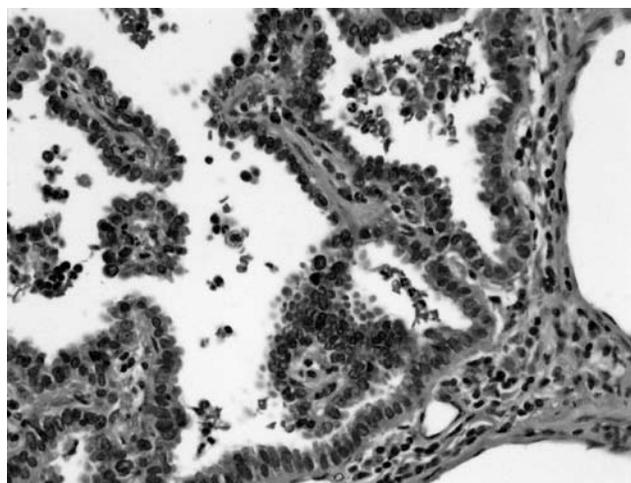


Fig. 4. Microscopic findings of the lung tumor. The monotonous and crowding tumor cells were lining according to the thickened alveolar septa (Case 3).

insertion in exon 20 (Case 3) were found in AD, but not in AAH. EGFR mutation was not found in osteosarcoma. Mutation of p53 in exon 7 was detected in osteosarcoma (Case 3). No other genomic mutations were detected.

Discussion

Lung cancer in young patients is very rare. Of 13,121 lung cancer patients who underwent surgery in Japan in 1999, only 23 (0.2%) were less than 30 years old.¹⁾ Of 627 patients with lung cancer or AAH of the lung treated operatively in our hospital from 1999 to 2008, only three under the age of 30 had osteosarcoma. These facts suggested a relationship between lung cancer and osteosarcoma in young patients.

Germline mutation of p53, such as Li-Fraumeni syndrome, which is characterized by multiple early-onset primary malignancy, was a candidate to cause both AD/AAH and osteosarcoma in the same person.^{3,4)} This hypothesis was partly supported by an immunohistochemical study of p53, but not by genomic analysis. EGFR mutation has an important role for carcinogenesis in some subsets of lung AD.⁵⁾ In osteosarcoma, EGFR mutation was also reported.⁶⁾ In this study, it was detected only in AD (Cases 1 and 3), but not in osteosarcoma.

Expression of HER-2 was reported in both lung cancer⁷⁾ and osteosarcoma.^{8,9)} K-ras and EGFR mutations were reported to exhibit a mutually exclusive pattern in lung AD.⁵⁾ Both HER-2 and K-ras were negative in the AD/AAH, but they were examined only in AD/AAH, not in

Table 1. Characteristics of immunohistochemical and genomic mutation analyses for osteosarcoma and lung tumor

Case	AD/AAH	Immunohistochemistry		Genomic mutations					
		Osteosarcoma	Lung tumor	Osteosarcoma		Lung tumor			
		p53	p53	EGFR	p53	EGFR	K-ras	HER-2	p53
1	AD	+	+	-	-	exon 19 delL747-T751	-	-	-
2	AAH	-	-	-	-	-	-	-	-
3	AD	+	+	-	exon 7	exon 20 insQ773-V774	-	-	-

AD: adenocarcinoma; AAH: atypical adenomatous hyperplasia; AD/AAH: AD or AAH; EGFR: epidermal growth factor receptor; HER-2: human epidermal growth factor receptor 2; del: deletion; ins: insertion; L:Lysine; T: Threonine; Q: Glutamine; V: Valine

osteosarcoma. Although our immunohistochemical and genomic exploration for a common oncogenic pathway of AD/AAH and osteosarcoma was limited, none may be apparent.

Chemotherapy was thought to have no role for these cases of AD/AAH because they were detected before chemotherapy for osteosarcoma was initiated.

Although we could not deny the existence of a common oncogenic pathway between lung cancer and osteosarcoma, the use of CT to screen for lung metastasis from osteosarcoma was thought to contribute in large part to the detection of AD/AAH in young patients under the age of 30 in this study. Thus the number of young patients with lung cancer might be higher than previously reported.¹⁾

References

1. Japanese Joint Committee of lung cancer. Lung cancer in Japan. Analysis of lung cancer registry for resected cases in 1999. (in Japanese) *Jpn J Lung Cancer* 2007; **47**: 299–311.
2. Kobayashi H, Mori T, Yoshioka M, Tanaka M, Okuma T, et al. A-14-year-old boy with small primary lung cancer. (in Japanese) *Jpn J Chest Surg* 1999; **13**: 144–7.
3. Kimura K, Shinmura K, Hasegawa T, Beppu Y, Yokoyama R, et al. Germline mutation in a patients with multiple primary cancers. *Jpn J Clin Oncol* 2001; **31**: 349–51.
4. Izawa N, Matsumoto S, Manabe J, Tanizawa T, Hoshi M, et al. A Japanese patient with Li-Fraumeni syndrome who had nine primary malignancies associated with a germline mutation of the p53 tumor-suppressor gene. *Int J Clin Oncol* 2008; **13**: 78–82.
5. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, et al. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res* 2004; **64**: 8919–23.
6. Wen YH, Koeppen H, Garcia R, Chiriboga L, Tarlow BD, et al. Epidermal growth factor receptor in osteosarcoma: expression and mutational analysis. *Hum Pathol* 2007; **38**: 1184–91.
7. Hirsch FR, Varella-Garcia M, Franklin WA, Veve R, Chen L, et al. Evaluation of HER-2/neu gene amplification and protein expression in non-small cell lung carcinomas. *Br J Cancer* 2002; **86**: 1449–56.
8. Onda M, Matsuda S, Higaki S, Iijima T, Fukushima J, et al. ErbB-2 expression is correlated with poor prognosis for patients with osteosarcoma. *Cancer* 1996; **77**: 71–8.
9. Gorlick R, Huvos AG, Heller G, Aledo A, Beardsley GP, et al. Expression of HER-2/erbB-2 correlates with survival in osteosarcoma. *J Clin Oncol* 1999; **17**: 2781–8.