Elmer Press

Case Report J Med Cases. 2016;7(11):484-487

Primary Lung Adenocarcinoma With Trophoblastic Differentiation and Usage of Gefitinib for Postoperative Recurrence: Report of a Case With a Review of the Literature

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Abstract

We report a rare and very aggressive case of lung carcinoma showing trophoblastic differentiation, so-called choriocarcinoma, for which postoperative recurrence was treated using gefitinib. A 51-year-old woman with pathological stage IIA adenocarcinoma with trophoblastic differentiation underwent left lower lobectomy with lymph node dissection and postoperative adjuvant chemotherapy, remaining tumor-free for 10 months until the detection of the brain metastasis. Gefitinib was administered, as the tumor was positive for epidermal growth factor receptor mutation, and this resulted in a 12-month progression-free period. The patient died 37 months after surgery due to multiple metastases in the brain, ovary and uterus. This is the first case report using gefitinib to the lung carcinoma showing trophoblastic differentiation. A review of the literature on lung cancer with trophoblastic differentiation suggested that a chemotherapeutic regimen for primary lung cancer other than germ cell tumor might be suitable for the lung carcinoma with trophoblastic differentiation.

Keywords: Lung cancer; Adenocarcinoma; Trophoblastic differentiation; Gefitinib; Choriocarcinoma

Introduction

We report a case of the lung carcinoma with trophoblastic differentiation so-called choriocarcinoma of the lung, of which the postoperative recurrence was treated by gefitinib. This carcinoma was very aggressive and we had difficulty selecting the chemotherapeutic agents for the treatment of the postoperative recurrences, therefore, we reviewed the literatures concerning the chemotherapeutic regimen of the lung carcinoma with trophoblastic differentiation or the choriocarcinoma of the lung.

Case Report

A 51-year-old woman visited us because of a nodular shadow in the left lung without any subjective symptoms. Physical examination was normal. She had never smoked and had no history of abnormal pregnancy or abortion. Laboratory examinations demonstrated elevation of the serum level of carcinoembryonic antigen (CEA) at 31.1 ng/mL and SLX at 45.8 U/mL. Chest X-ray and computed tomography (CT) demonstrated a nodule with spicula and pleural indentation in the left S6 without lymphadenopathy (Fig. 1a, b). CT-guided needle biopsy revealed poorly differentiated adenocarcinoma with partial trophoblastic differentiation. Gynecological examination including magnetic resonance imaging (MRI) revealed no abnormality except for a uterine leiomyoma and an elevated serum level of hCG at 4.9 mIU/mL (SV 1.0). No distant metastasis was detected by abdominal CT, brain MRI and bone scintigraphy. The clinical stage of this tumor was cT1bN0M0 stage IA.

Left lower lobectomy and lymph node dissection was performed in December 2009. Pathological examination revealed that the tumor was 26 × 24 mm in size without pleural invasion and the interlobular lymph node was involved. Therefore, the postoperative staging was revised to pT1bN1M0 stage IIA. Light microscopy revealed that the tumor had two different histological components: mixed adenocarcinoma showing solid with mucinous or acinar adenocarcinoma, and trophoblastic differentiation with syncytiotrophoblast-like multinucleated giant cells (Fig. 2a, b). Immunohistological examination demonstrated diffuse positivity for CK7, CEA, IMP-3, Ki67 and TTF-1, but negativity for CK20. The hCG-positive cells were scattered in both the area of adenocarcinoma and trophoblastic differentiation.

Postoperative adjuvant chemotherapy was administrated with four cycles of carboplatin and paclitaxel. The serum level of hCG decreased to 3.4 mIU/mL being the minimum value throughout the observation period. In October 2010, brain MRI revealed three metastases when the serum level of hCG had increased to 5.0 mIU/mL, and gamma-knife therapy was

Manuscript accepted for publication October 10, 2016

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doi: http://dx.doi.org/10.14740/jmc2662w

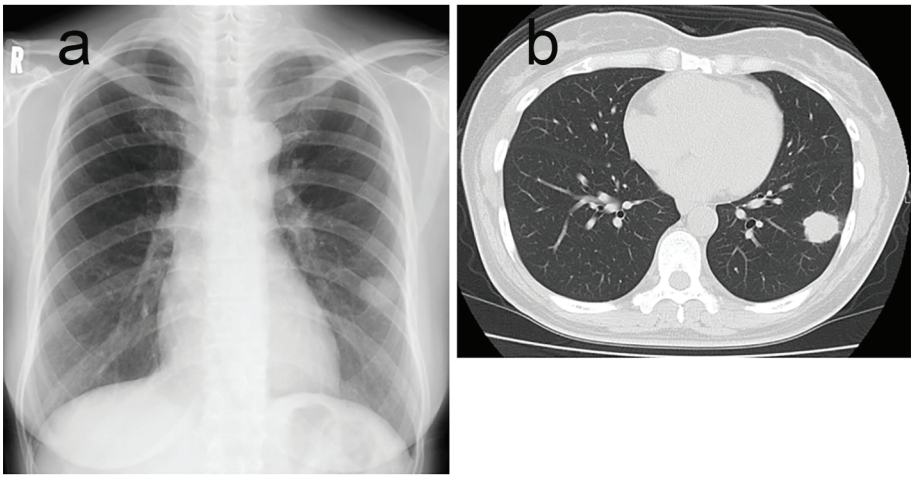

Figure 1. Preoperative chest X-ray showing a 2.5-cm round shadow in the left lung (a). CT revealed spicula and pleural indentation in S6 (b).

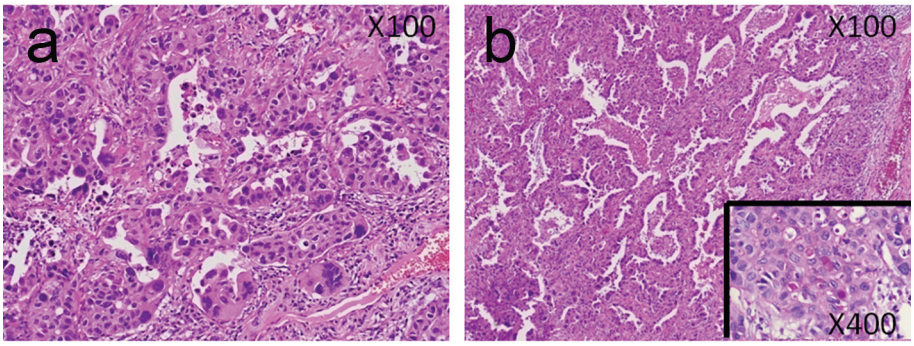

Figure 2. Pathological examination demonstrated mixed adenocarcinoma with trophoblastic differentiation (a), and acinar-type non-mucous bronchioloalveolar carcinoma (b).

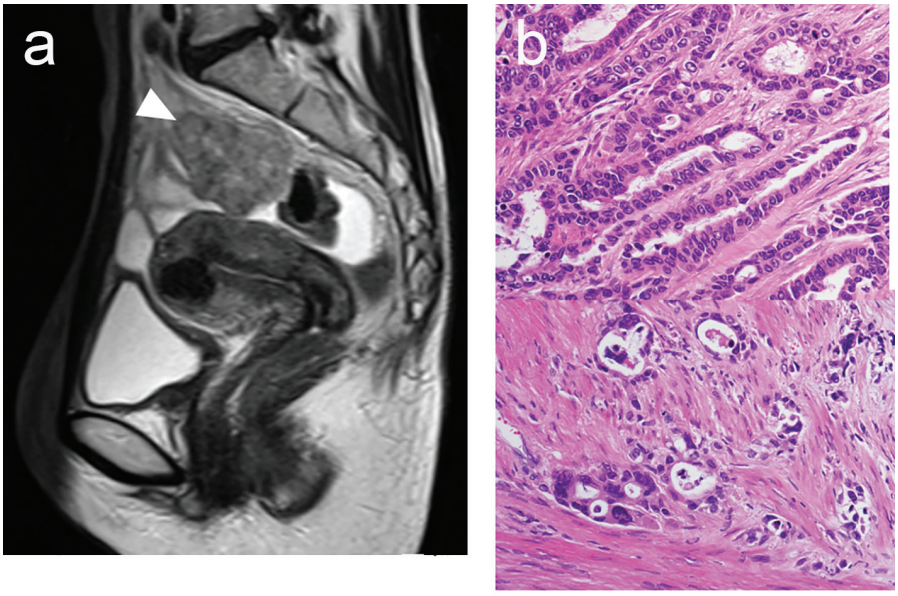

Figure 3. MRI in June 2012 revealed metastases in the right ovary and uterus (arrowhead) (a). Necropsy of the ovary metastasis demonstrated adenocarcinoma accompanied by trophoblastic differentiation (b).

Table 1. The Cases of Lung Carcinoma With Trophoblastic Differentiation or Choriocarcinoma of the Lung

Year	Age	Gender	T	N	M	Stage	Operative procedure	Chemotherapy regimen	Combined cancer	Observation period (months)	Cause of death
1952	NA	F	4	NA	1b	IV	PN	ND	ND	0	TR
1954	29	F	3	2	NA	NA	PN	ND	NBC	3	TD
1977	45	M	NA	NA	NA	NA	-	ND	GCC	5	TD
1977	57	M	NA	3	NA	NA	-	ND	GCC	12	TD
1979	63	M	NA	3	NA	NA	-	5FU + CTX	Sm	2	TD
1980	27	M	NA	0	0	NA	LB	PVP	NBC	4	Alive
1982	67	M	3	NA	NA	NA	LB	ND	NBC	36	Alive
1983	22	F	3	NA	1b	IV	-	ND	ND	0	TD
1985	34	F	2a	0	0	IB	LB	UD	NBC	6	Alive
1987	60	F	3	2	0	IIIA	PN	ND	ND	0	TD
1988	21	F	NA	NA	1b	IV	-	MA-CO	ND	NA	TD
1989	51	M	3	2	1b	IV	-	ND	Non-Ad non-Sq	0	TD
1989	37	M	3	2	0	IIIA	PN	PE	La	15	TD
1990	68	M	3	NA	0	IIB-IIIB	LB	MAC, PE, PACE	La	15	Alive
1992	55	F	NA	NA	0	NA	LB	ND	La	NA	Alive
1992	59	F	NA	NA	1b	IV	-	MAC	ND	5	TD
1994	61	M	2b	0	0	IIA	PN	PVP or VPV	NBC	1.5	TR
1994	NA	M	2b	0	0	NA	LB	PVP	NBC	5	TD
1994	27	F	1b	NA	0	IA	LB	EMA, PE	Ad	36	Alive
1995	69	M	NA	NA	1b	IV	-	UD	NBC	1.5	TD
1996	54	F	3	NA	1b	IV	LB	BOMP/EPI	ND	12	Alive
1996	29	F		NA	0	NA	-	BEP, CHAMOCA, MTX	ND	72	Alive
1996	69	M	2a	0	0	IB	LB	BEP	NBC	6	Alive
1997	69	M	3	NA	1b	IV	-	ND	La and UDC	0	ND
2000	60	M	2	0	0	IB or IIA	-	UD	NBC	5	TD
2000	61	M	2	0	0	IB or IIA	LB	ND	GCC	5	TD
2001	61	M	NA	NA	NA	NA	WR	BEP, EMA/CO	Ad	6	Alive
2001	58	M	NA	2	0	NA	LB	ND	La	5	TD
2002	23	M	NA	NA	1a	IV	-	MAC	NBC	0	TD
2003	37	F	NA	NA	NA	NA	LB	BEP	NBC	12	Alive
2006	77	M	2b	3	1b	IV	-	ND	Ad and UDC	0	TD

F: female; M: male; NA: not available; PN: pneumonectomy; LB: lobectomy; WR: wedge resection; ND: no description; 5FU: 5-flourouracil; CTX: cyclophosphamide; PVP: cisplatin and etoposide; MA-CO: methotrexate, actinomycin D/oncovin, cyclophosphamide; PE: etoposide and cisplatin; MAC: methotrexate/leucovorin, actinomycin-D, and cyclophosphamide or chlorambucil; PACE: cisplatin, adriamycin and cytoxan; VPV: bleomycin by vinblastine; EMA: etoposide and cisplatin/etoposide, methotrexate, and actinomycin D; BOMP-EPI: bleomycin, vincristine, methotrexate, platinum/etoposide, platinum, ifosfamide; BEP: bleomycin, etoposide, cisplatin; CHAMOCA: cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan and vincristine; MTX: methotrexate; UD: unknown details; NBC: nothing but choriocarcinoma; GCC: giant cell carcinoma; Sm: small cell carcinoma; Ad: adenocarcinoma; Sq: squamous cell carcinoma; La: large cell carcinoma; UDC: undifferentiated carcinoma; TR: treatment-related death; TD: tumor death.

administrated. However, 2 months later, MRI demonstrated newly developed multiple brain metastases, and 30 Gy of whole-brain irradiation was performed. Despite these treatments, the serum level of hCG increased to 6.5 mIU/mL. The L858R mutation of exon21 in the EGFR gene was confirmed, and gefitinib was administered at 250 mg/day through June 2011 until June 2012 without any severe adverse reaction except for grade 2 dermatitis. By December 2011, the serum level of hCG had decreased to 4.1 mIU/mL. In May 2012, the serum level of hCG was 4.3 mIU/mL, and FDG-PET and abdominal MRI revealed newly developed metastases in the right ovary and uterus in June 2012 (Fig. 3a). Combination chemotherapy with cisplatin and pemetrexed was administered, but the second cycle had to be suspended due to grade 3 hyponatremia. Pemetrexed was then administered as a single agent, but hyponatremia and performance status 4 also disturbed the second cycle or any further anti-cancer therapy. The patient died in January 2013, and necropsy of the right

ovarian metastasis revealed invasive proliferation of adenocarcinoma with trophoblastic differentiation and positivity for TTF-1 and hCG (Fig. 3b).

Discussion

The serum level of hCG was an accurate indicator of tumor aggravation which was 4.9, 3.4, 5.0 and 4.1 mIU/mL in the preoperative period, during postoperative adjuvant chemotherapy, and when brain metastasis was first detected and gefitinib therapy initiated, respectively.

Complete resection and standard adjuvant chemotherapy resulted in a 10-month postoperative tumor-free period, and gefitinib therapy, believed to prolong the median progression-free period approximately 9.5 months among the epidermal growth factor receptor mutant positive non-small lung cancer patients, achieved a 12-month progression-free period in this case after recurrence [1]. To our best knowledge, this is the first report to describe the effects of gefitinib for primary lung adenocarcinoma with trophoblastic differentiation.

In the latest WHO classification, the term primary choriocarcinoma of the lung was thought to be contradictory [2]. Table 1 lists 31 cases of lung carcinoma with trophoblastic differentiation, or the choriocarcinoma of the lung, retrieved from the English literature [3-8]. For 18 of the 31 cases, including duplicates, anti-cancer chemotherapy was employed using the regimens shown in Table 1. All of these regimens were regarded as the appropriate protocol for germ cell tumors, except for PE and PACE which are currently appropriate protocols for small cell carcinoma of the lung. The three patients who received PE or PACE survived for more than 15 months. The remaining 14 patients treated with protocols for germ cell tumor died within 12 months except one case. These results suggest that chemotherapy regimens for primary lung cancer other than germ cell tumor might be suitable for the lung carcinoma with trophoblastic differentiation.

Conclusion

We have reported a case of lung adenocarcinoma with trophoblastic differentiation. Complete resection and adjuvant chemotherapy achieved a 10-month tumor-free period, and use of gefitinib led to a 12-month progression-free period.

Conflicts of Interest

Yasumichi Yamamoto, Toshiya Toyazaki and Shinji Kosaka have no conflicts of interest.

Grant or Financial Support

None.

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