

Figure 2 CT scan showing improvement in consolidation after four courses of chemotherapy.

dihydroxypyridine (CDHP) and potassium oxonate at a fixed molar ratio of 1 : 0.4 : 1.⁷ Tegafur is a pro-drug of fluorouracil (5-FU), which is the cytotoxic component of this combination. CDHP is a potent reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), the chief catabolic enzyme of 5-FU. Potassium oxonate selectively inhibits orotate phosphoribosyl-transferase, the enzyme responsible for 5-FU activation in the gastrointestinal tract, thus reducing the gastrointestinal toxicity of the combination.

S-1 is active against advanced NSCLC.^{8,9} In the phase II trial, the overall response rate was 22% and the median survival was 10 months for previously untreated NSCLC patients.⁸ The effectiveness of S-1 for BAC, however, has not been evaluated. Grade 3 or 4 toxicities to S-1 were seen in a relatively low percentage of patients: decreased Hb in 1.7%, neutropaenia in 6.8%, thrombocytopaenia in 1.7%, anorexia in 10.2%, diarrhoea in 8.5%, stomatitis in 1.7% and malaise in 6.8%.⁸ In the present patient, no serious adverse events were observed, but she suffered grade 1 anorexia.

The patient presented here had a partial response to S-1, resulting in respiratory symptom improvement and weaning from oxygen supplementation. This is the first report of successfully treated refractory BAC with S-1 and suggests that S-1 is an attractive option for the treatment of advanced BAC.

ACKNOWLEDGEMENT

We thank Dr Hiroshi Kubo (Tohoku University School of Medicine) for comments and discussion.

REFERENCES

- 1 Barkley JE, Green MR. Bronchioloalveolar carcinoma. *J. Clin. Oncol.* 1996; **14**: 2377–86.
- 2 Miller VA, Hirsch FR, Johnson DH. Systemic therapy of advanced bronchioloalveolar cell carcinoma: challenges and opportunities. *J. Clin. Oncol.* 2005; **23**: 3288–93.

- 3 West HL, Crowley JJ, Vance RB, Franklin WA, Livingston RB *et al.* Advanced bronchioloalveolar carcinoma: a phase II trial of paclitaxel by 96-hour infusion (SWOG 9714): a Southwest Oncology Group trial. *Ann. Oncol.* 2005; **16**: 1076–80.
- 4 Yano S, Kanematsu T, Miki T, Aono Y, Azuma M *et al.* A report of two bronchioloalveolar carcinoma cases which were rapidly improved by treatment with the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 ('Iressa'). *Cancer Sci.* 2003; **94**: 453–8.
- 5 Kitazaki T, Fukuda M, Soda H, Kohno S. Novel effects of gefitinib on mucin production in bronchioloalveolar carcinoma; two case reports. *Lung Cancer* 2005; **49**: 125–8.
- 6 West HL, Franklin WA, McCoy J, Gumerlock PH, Vance R *et al.* Gefitinib therapy in advanced bronchioloalveolar carcinoma: Southwest Oncology Group Study S0126. *J. Clin. Oncol.* 2006; **24**: 1807–13.
- 7 Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res.* 1993; **53**: 4004–9.
- 8 Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K *et al.* Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br. J. Cancer* 2001; **85**: 939–43.
- 9 Ichinose Y, Yoshimori K, Sakai H, Nakai Y, Sugiura T *et al.* S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. *Clin. Cancer Res.* 2004; **10**: 7860–4.

Correspondence: Seiichi Kobayashi, Department of Respiratory Medicine, Japanese Red Cross Ishinomaki Hospital, 71 Nishimichishita, Hebata, Ishinomaki 986-8522, Japan. Email: skoba-thk@umin.ac.jp

Prostatic metastasis of large cell neuroendocrine carcinoma of the lung

JEONG HWAN YOO,¹ JI HYUN LEE,²
EUN KYUNG KIM,² YOUNG KWON HONG,³
YONGHEE LEE⁴ AND HYE CHEOL JEONG²

¹Department of Internal Medicine, Divisions of
²Pulmonary and Critical Care Medicine, ³Urology and
⁴Pathology, Bundang CHA hospital, College of
Medicine, Pochon CHA University, Seongnam-city,
Korea

ABSTRACT

Large cell neuroendocrine carcinoma (LCNEC) of the lung is a rare and aggressive tumour with a poor prognosis. Lung cancer metastases to the prostate are also uncommon, and are usually found incidentally during autopsy. Most reported primary lung cancers with prostatic metastases are small cell carcinomas, and prostatic metastases from LCNEC of the lung have not been reported previously. This case report describes a 70-year-old man with LCNEC of the lung and metastases in the prostate, brain, bone, liver and lymph nodes.

Key words: large cell neuroendocrine carcinoma, lung cancer, metastasis, prostate.

INTRODUCTION

Lung cancer can spread to any organ, but metastases to the prostate have rarely been reported.¹⁻³ Metastatic cancer of the prostate occurs mostly by direct local invasion from adjacent organs such as the bladder or rectum. Metastatic cancer of the prostate from a distant primary tumour has most commonly been associated with lung cancer.¹ Of the primary lung cancers reported as having spread to the prostate, most are small cell carcinomas, with a few poorly differentiated large cell carcinomas also being described. There are no previous reports of prostatic metastases from primary LCNEC of the lung.

CASE REPORT

A 70-year-old man with no previous disease history presented with difficulty in voiding, dyspnoea on exertion, a non-productive cough and unintentional weight loss of 2 kg over the previous 3 months. He had stopped smoking 25 years previously and had a 10-pack-year smoking history. Physical examination revealed painless lymphadenopathy in the right supraclavicular fossa. Laboratory investigations were normal apart from a raised LDH (1241 U/L). Urinalysis revealed microscopic haematuria. CXR showed a mass of approximately 7 cm diameter in the left upper lobe. Chest CT revealed a lung mass with enlarged bilateral paratracheal, bilateral hilar and subcarinal lymph nodes (Fig. 1a). Bronchoscopy was normal. Ultrasonography-guided cervical lymph node biopsy suggested metastatic carcinoma. Brain MRI and PET scan were performed for staging. Brain MRI revealed multiple metastatic nodules. PET revealed a focal mass with strong FDG uptake in the left lobe and multiple FDG uptakes in the sternum, pelvic bones, liver, right cervical, bilateral paratracheal, bilateral hilar and subcarinal lymph nodes, as well as strong focal uptake in the prostate (Fig. 1b).

Palliative radiotherapy to the brain was performed. The patient complained of persistent difficulty in voiding and haematuria. Transurethral resection of the prostate was performed for symptom control and the resected tissue showed neuroendocrine features on light microscopy (Fig. 2a). On immunohisto-

chemistry, the tumour cells showed positive reactions for synaptophysin, chromogranin A, cytokeratin 7 (CK7) and thyroid transcription factor-1 (Fig. 2b-d). Immunohistochemical staining for prostate-specific acid phosphatase (PSAP), P504S/alpha methylacyl CoA racemase (AMACR), prostate-specific antigen (PSA), CK20, CD56 and the p63 gene was negative. These findings were similar to those of the cervical lymph node biopsy specimen.

One cycle of chemotherapy with paclitaxel was performed, but hypercalcaemia (15.6 mg/dL) developed and the patient deteriorated and died 6 days later.

DISCUSSION

In 1991, LCNEC of the lung was first proposed as a fourth type of pulmonary neuroendocrine tumour.^{4,5} Although LCNEC has been increasingly recognized in recent years, its incidence remains low. Fernandez *et al.* reported that the prevalence of LCNEC in surgically resected lung cancers was between 2.1% and 3.5%.⁶⁻¹¹ Metastatic cancers in the prostate are also uncommon, and are usually found incidentally during autopsy.^{12,13} Prostatic involvement in metastatic disease appears to be a late phenomenon. Most patients with metastatic prostate cancer have had carcinomatosis or widely disseminated malignancy.^{1,13} LCNEC is clinically aggressive and has a very poor prognosis.^{6-11,14} As a result, it is possible that prostatic metastases could occur in patients with LCNEC of the lung.

In this patient, it was difficult to tell if the primary LCNEC tumour had originated in the lung or the prostate; however, the evidence would tend to implicate the lung. First, pulmonary neuroendocrine tumours are more common than prostatic neuroendocrine tumours, with prostatic neuroendocrine carcinomas accounting for 1-5% of all prostate cancers.¹⁵ Although LCNEC of the prostate has been underdiagnosed, Evans *et al.* identified only seven cases of LCNEC occurring in the prostate.¹⁶ Second, prostate cancer can metastasize by direct local invasion, haematogenous and lymphatic spread. Haematogenous metastases of prostate cancer are frequently to the bone, notably the spine. Bubendorf *et al.* reported a gradual decline in the frequency of

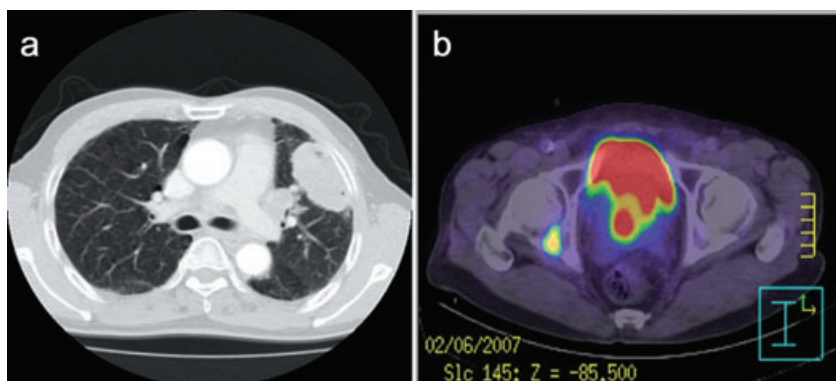


Figure 1 (a) Chest CT shows a tumour mass in the left lingular segment. (b) PET shows strong focal uptake in the prostate.

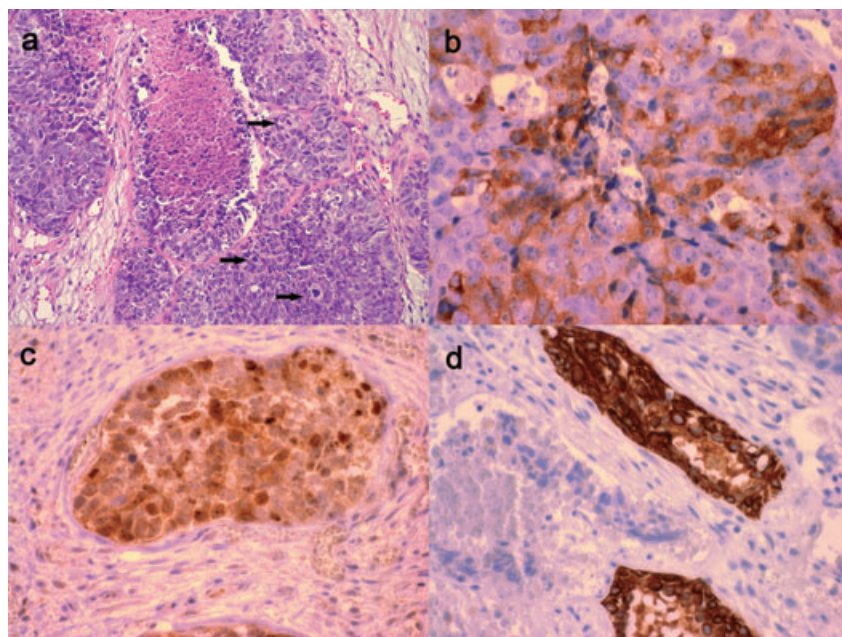


Figure 2 (a) Prostatic biopsy showing organoid nesting tumour cells with necrosis and frequent mitoses (average 150–160 mitotic figures/10 high power fields) (arrow). Those cells have vesicular fine chromatin, large cell size and frequent nucleoli (original magnification $\times 200$). Positive immunohistochemical staining for (b) synaptophysin, (c) chromogranin A and (d) CK7.

metastases of prostate cancer from the lumbar to the cervical spine, suggesting an initial lumbar metastasis and subsequent upward spread.¹⁷ The lung is also a frequent site of prostate cancer metastases, but lung involvement is usually associated with large prostatic cancers.¹⁷ Lymphatic spread of prostatic cancer commonly involves the obturator node, followed by the perivesical, hypogastric, iliac, presacral and paraaortic nodes.^{18,19} In this patient, we were unable to find any evidence of prostatic cancer metastases in these sites. Finally, PSAP and P504S/AMACR are relatively specific for LCNEC of the prostate,¹⁵ and in this patient, immunohistochemical staining for PSAP and P504S/AMACR was negative.

In conclusion, prostatic metastases from LCNEC of the lung are associated with widely disseminated malignancy and rarely occur; however, differentiation from primary prostate cancer with pulmonary metastases is required. Diagnostic criteria for LCNEC and neuroendocrine markers, which clearly identify the primary site of a metastatic cancer, are required.

REFERENCES

- Bates AW, Baithun SI. Secondary solid neoplasms of the prostate: a clinico-pathological series of 51 cases. *Virchows Arch.* 2002; **440**: 392–6.
- Madersbacher S, Schatzl G, Susani M, Maier U. Prostatic metastasis of a small cell lung cancer in a young male. *Eur. Urol.* 1994; **26**: 267–9.
- Smedley HM, Brown C, Turner A. Ectopic ACTH-producing lung cancer presenting with prostatic metastasis. *Postgrad. Med. J.* 1983; **59**: 371–2.
- Travis WD, Linnoila RI, Tsokos MG, Hitchcock CL, Cutler GB Jr *et al.* Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma: an ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am. J. Surg. Pathol.* 1991; **15**: 529–53.
- Travis WD, Rush W, Flieder DB, Falk R, Fleming MV *et al.* Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. *Am. J. Surg. Pathol.* 1998; **22**: 934–44.
- Jiang SX, Kameya T, Shoji M, Dobashi Y, Shinada J *et al.* Large cell neuroendocrine carcinoma of the lung: a histologic and immunohistochemical study of 22 cases. *Am. J. Surg. Pathol.* 1998; **22**: 526–37.
- Takei H, Asamura H, Maeshima A, Suzuki K, Kondo H *et al.* Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty-seven cases. *J. Thorac. Cardiovasc. Surg.* 2002; **124**: 285–92.
- Iyoda A, Hiroshima K, Toyozaki T, Haga Y, Fujisawa T *et al.* Clinical characterization of pulmonary large cell neuroendocrine carcinoma and large cell carcinoma with neuroendocrine morphology. *Cancer* 2001; **91**: 1992–2000.
- Paci M, Cavazza A, Annessi V, Putrino I, Ferrari G *et al.* Large cell neuroendocrine carcinoma of the lung: a 10-year clinicopathologic retrospective study. *Ann. Thorac. Surg.* 2004; **77**: 1163–7.
- Battafarano RJ, Fernandez FG, Ritter J, Meyers BF, Guthrie TJ *et al.* Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer. *J. Thorac. Cardiovasc. Surg.* 2005; **130**: 166–72.
- Fernandez FG, Battafarano RJ. Large-cell neuroendocrine carcinoma of the lung. *Cancer Control* 2006; **13**: 270–5.
- Johnson DE, Chalbaum R, Ayala AG. Secondary tumours of the prostate. *J. Urol.* 1974; **112**: 507–8.
- Zein TA, Huben R, Lane W, Pontes JE, Englander LS. Secondary tumours of the prostate. *J. Urol.* 1955; **133**: 615–16.
- Veronesi G, Morandi U, Alloisio M, Terzi A, Cardillo G *et al.* Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases. *Lung Cancer* 2006; **53**: 111–15.
- Evans AJ, Humphrey PA, Belani J, van der Kwast TH, Srigley JR. Large cell neuroendocrine carcinoma of prostate: a clinicopathologic summary of 7 cases of a rare manifestation of advanced prostate cancer. *Am. J. Surg. Pathol.* 2006; **30**: 684–93.
- Fernandes RC, Matsushita MM, Mauad T, Nascimento Saldiva PH. Prostate carcinoma with neuroendocrine differentiation: case report and literature review. *Rev. Hosp. Clin. Fac. Med. Sao Paulo* 2001; **56**: 153–8.

- 17 Bubendorf L, Schopfer A, Wagner U, Sauter G, Moch H *et al.* Metastatic patterns of prostate cancer: an autopsy study of 1589 patients. *Hum. Pathol.* 2000; **31**: 578–83.
- 18 Donohue RE, Pfister RR, Weigel JW, Stonington OG. Pelvic lymphadenectomy in stage A prostatic cancer. *Urology* 1977; **9**: 273–5.
- 19 Wilson CS, Dahl DS, Middleton RG. Pelvic lymphadenectomy for the staging of apparently localized prostatic cancer. *J. Urol.* 1977; **117**: 197–8.

Correspondence: Hye Cheol Jeong, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Bundang CHA Hospital, College of Medicine, Pochon CHA University, 351, Yatap-dong, Bundang-gu, Seongnam-city, Kyeonggi-do 463-712, Korea. Email: jhcmed@hanmail.net

Spontaneous pneumothorax due to Birt-Hogg-Dube syndrome in a Chinese family

SHUN-YANG SO

Department of Medicine, University of Hong Kong, Hong Kong, China

ABSTRACT

A Chinese woman presented with a spontaneous pneumothorax and a family history suggestive of the autosomal dominant transmission of pneumothorax. The patient also had skin fibrofolliculomas and folliculin gene deletion, compatible with Birt-Hogg-Dube (BHD) syndrome. The importance of BHD syndrome and other familial spontaneous pneumothoraces is discussed.

Key words: folliculin, pneumothorax, pulmonary cyst.

CASE REPORT

A 57-year-old Chinese woman suffered a spontaneous pneumothorax in 1997. At video-assisted thoracoscopic pleurodesis, multiple cysts 1–4 cm in diameter, mainly in the lower lobe of the lung, were found.

Chest CT revealed bilateral lung cysts with a peripheral and basal distribution (Fig. 1). Catamenial pneumothorax was unlikely as a total hysterectomy and bilateral salpingo-oophorectomy for endometriosis had been performed 12 years prior to the initial pneumothorax. There were no clinical features suggestive of Marfan syndrome or tuberous sclerosis. Her FEV₁/FVC was 1.93/2.21 l. = 87%. No cause was found for her pneumothorax.

There was, however, a strong family history of spontaneous pneumothorax, which was suggestive of an autosomal dominant transmission (Fig. 2).

In 2005 the patient consulted a dermatologist for assessment of white papules near her nose. Skin biopsy revealed fibrofolliculomata and BHD syndrome was suspected. Ultrasound showed no renal tumours. Blood DNA analysis showed deletion of three bases (del AAG) from nucleotides 1522 to 1524 of the folliculin gene which resulted in deletion of a codon for lysine at position 508 (del K508) in the encoded mRNA. The same mutation was found in the patient's two daughters who also had suffered pneumothoraces. Such a deletion of folliculin gene, though not previously reported, is compatible with BHD syndrome.

DISCUSSION

Birt-Hogg-Dube syndrome is a dominantly inherited condition characterized by three main features:

1 Fibrofolliculomata and other less common benign skin tumours such as trichodiscoma and acrochordon.¹ Fibrofolliculomata are small, non-itchy white papules found over the face, neck and upper chest.

2 Multiple lung cysts and spontaneous pneumothoraces.²

3 Renal tumours, which are typically bilateral and multiple with mixed histology.³

The majority of patients with BHD syndrome have a mutation of the folliculin gene.⁴ Folliculin is strongly expressed in the lung (in fibroblasts and macrophages), skin and kidneys.⁵ Folliculin may be a tumour suppressor gene acting through activation of the mammalian target of rapamycin carcinogenic

Table 1 The molecular basis of inherited spontaneous pneumothorax

Disease	Gene(s) and gene product	Chromosomal location	Potential treatment
Marfan syndrome	FBN1 (Fibrillin 1)	15q21.1	Losartan
Homocystinuria	CBS (Cystathionine β-synthase)	21q22.3	Pyridoxine
Vascular Ehlers-Danlos syndrome	COL3A1 (type 3 collagen)	2q31	
Lymphangioleiomyomatosis (LAM)	TSC1 (Hamartin) and TSC2 (Tuberin)	9q34,16p13	Sirolimus
α1-antitrypsin deficiency	PI (α1-antitrypsin)	14q32.1	α1-antitrypsin
BHD syndrome	FLCN or BHD (Folliculin)	17p11.2	
Isolated familial spontaneous pneumothorax	FLCN or BHD (Folliculin)	17p11.2	

BHD, Birt-Hogg-Dube.