Primary Pulmonary T-cell Lymphoma in an HTLV-1 Carrier

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ABSTRACT —— ***Background.*** The incidence of primary pulmonary lymphomas is only 0.34%, and peripheral T-cell lymphoma is very rare. Moreover, there is no literature recording its appearance in a Human T lymphotropic virus type 1 (HTLV-1) carrier. ***Case.*** A 65-year old man with dry cough, fever, and chills was admitted with multiple pulmonary nodules and pleural effusion. High lymphocyte count and elevated adenosine deaminase (ADA) were found in the pleural effusion. Antitubercular therapy yielded no clinical or radiologic improvement. The patient was transferred to our hospital where lymphoma was confirmed from positive rearrangement of the TCR-β gene in cells in the pleural effusion. The patient was positive for HTLV-1 antibody, but did not have monoclonal integration of the pro-virus HTLV-1 in cells in the pleural effusion. ***Conclusion.*** This was the first case of an HTLV-1 carrier presenting with primary pulmonary T cell lymphoma. (*JJLC.* 2005;45:25-30)

KEY WORDS —— Human T lymphotropic virus type-1 (HTLV-1), Primary pulmonary T-cell lymphoma

INTRODUCTION

Lymphomas in the lung are often reported, with pleural involvement in about 20% of cases,[1] however primary pulmonary lymphomas are rare.[2] The incidence is 0.34%,[3] and overall the tumors have been estimated to comprise only 3% to 4% of all extranodal lymphomas.[4] Although a variety of morphologic subtypes can be seen in the tumors, the most common form of primary pulmonary lymphoma is B cell non-Hodgkin lymphoma (NHL); in the study of 62 cases of primary pulmonary lymphoma, 58 cases were B-cell lymphoma and only 2 cases were T-cell lymphomas.[5] While, HTLV-1 is highly endemic in southwestern Japan (Kagoshima, Miyazaki, Okinawa)[6] and is known to cause adult T-cell leukemia/lymphoma (ATL). The whole-life risk of ATL among persistent HTLV-1 carriers is estimated at 2% to 6%.[7] There is no literature recording primary pulmonary T-cell lymphoma in an HTLV-1 carrier, and ours is the first reported case.

CASE REPORT

In December 2002, a 65-year old man with dry cough, fever, and chills was admitted to a local hospital, where chest radiography revealed bilateral pulmonary nodules and pleural effusion. Initial examination of the effusion revealed high lymphocyte counts and an elevated adenosine deaminase (ADA) concentration; an antituberculosis drug was administered. However, there was no clinical or radiologic improvement, and the patient was transferred to our hospital on February 4, 2003. Physical examination revealed decreased respiratory sounds in the lower bilateral lungs. Hematologic examination showed a decrease in hemoglobin and platelet count (Table 1). Laboratory examination showed increased concentration of serum lactic dehydrogenase (LDH) 716 IU/*l* (normal, 279 to 491 IU/*l*), aspartate aminotransferase (AST) 75 IU/dl (normal, 13 to 34 IU/dl), and C-reactive protein (CRP) 6.99 mg/dl (normal, $<$0.3 mg/dl). Soluble interleukin-2 receptor (sIL-2R) was 3000 U/ml (normal, 220 to 530 U/ml), and HTLV-1 antibody was positive. Neuron-Specific Enolase (NSE) was elevated at 22.5 ng/ml (normal, 0.0 to 10.0 ng/ml), but Pro-Gastrin Releasing Peptide (ProGRP) was only 28.5 pg/ml (normal, $<$46 pg/ml). Chest radiography again revealed multiple nodules and bilateral pleural effusion, and computed tomography (CT) confirmed these findings (Figures, 1A and 2A). CT of the head and abdomen, and bone scintigram revealed no abnormalities. There was no palpable superficial

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Table 1. Laboratory Findings on Admission

Hematology		Serum chemistry		Pleural effusion	
WBC	4300 /μl	TP	5.6 g/dl	T.P	3.2 g/dl
Neut	91%	Alb	2.3 g/dl	LDH	2133 IU/l
Lymph	4%	LDH	716 IU/dl	Glu	51 mg/dl
Mono	5%	AST	75 IU/dl	ADA	150 IU/l
RBC	373 × 10^4/μl	ALT	32 IU/dl	sIL-2R	16143 U/ml
Hb	11.8 g/dl	T-Bil	1.1 mg/dl	Total cells	1700/μl
Plt	9.6 × 10^4/μl	T-cho	113 mg/dl	Neu	2%
		BUN	23 mg/dl	Mono	24%
Serology		Cr	0.8 mg/dl	Lymph	66%
CRP	6.99 mg/dl	Ca	7.4 mg/dl	Aty-Lymph	8%
ANA	(±)				
PR3-ANCA	< 10 EU	Tumor markers		Rearrangement of	
MPO-ANCA	< 10 EU	CEA	1.3 ng/ml	T-cell receptor Cβ1	positive
β-D-glucan	< 2.4 pg/ml	SCC	0.2 ng/ml		
Cryptococcal antigen	negative	NSE	22.5 ng/ml	Monoclonal integration	
HTLV-1 ab	positive	ProGRP	28.5 pg/ml	of pro-virus HTLV-1	negative
sIL-2R	3000 U/ml				

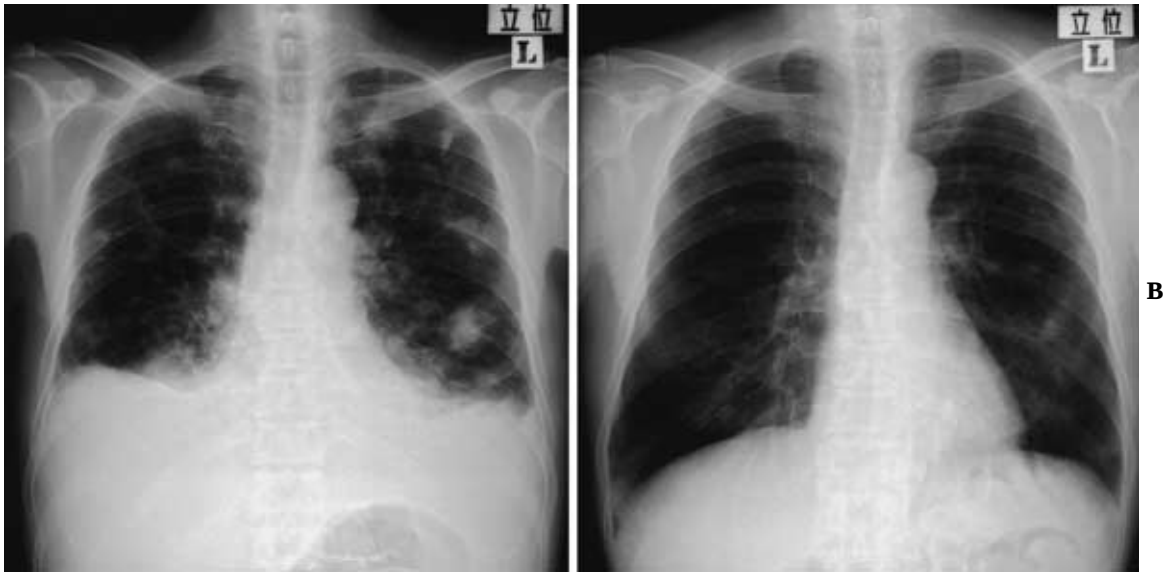

Figure 1. **A.** Chest radiography on admission, showing bilateral nodules and pleural effusion. **B.** Chest radiography 1 month after chemotherapy, showing a decrease in the nodules and effusion.

lymph node. Bone marrow aspiration did not show any abnormalities. These findings indicated the diseased lesion involved only the lung. The pleural effusion was re-examined. There were many lymphocytes (Table 1) and a high ADA concentration (150 IU/*l*). LDH and sIL-2R were also high. Cytologic examination of the fluid showed atypical lymphoid cells (Figure 3). Flow cytometric analysis of these cells (Table 2) revealed positive reaction for CD2, CD3, CD4, CD5 and CD7, and negative for CD8. Although the patient was positive for HTLV-1 antibody, Southern analysis of the cells did not reveal monoclonal integration of the pro-virus HTLV-1 (Figure 4). Monoclonal rearrangement of the TCR-β gene was detected (Figure 5). From these findings, the patient was diagnosed with peripheral T-cell lymphoma of the lung, and ATL was ruled out. He was treated with VCAP/AMP/

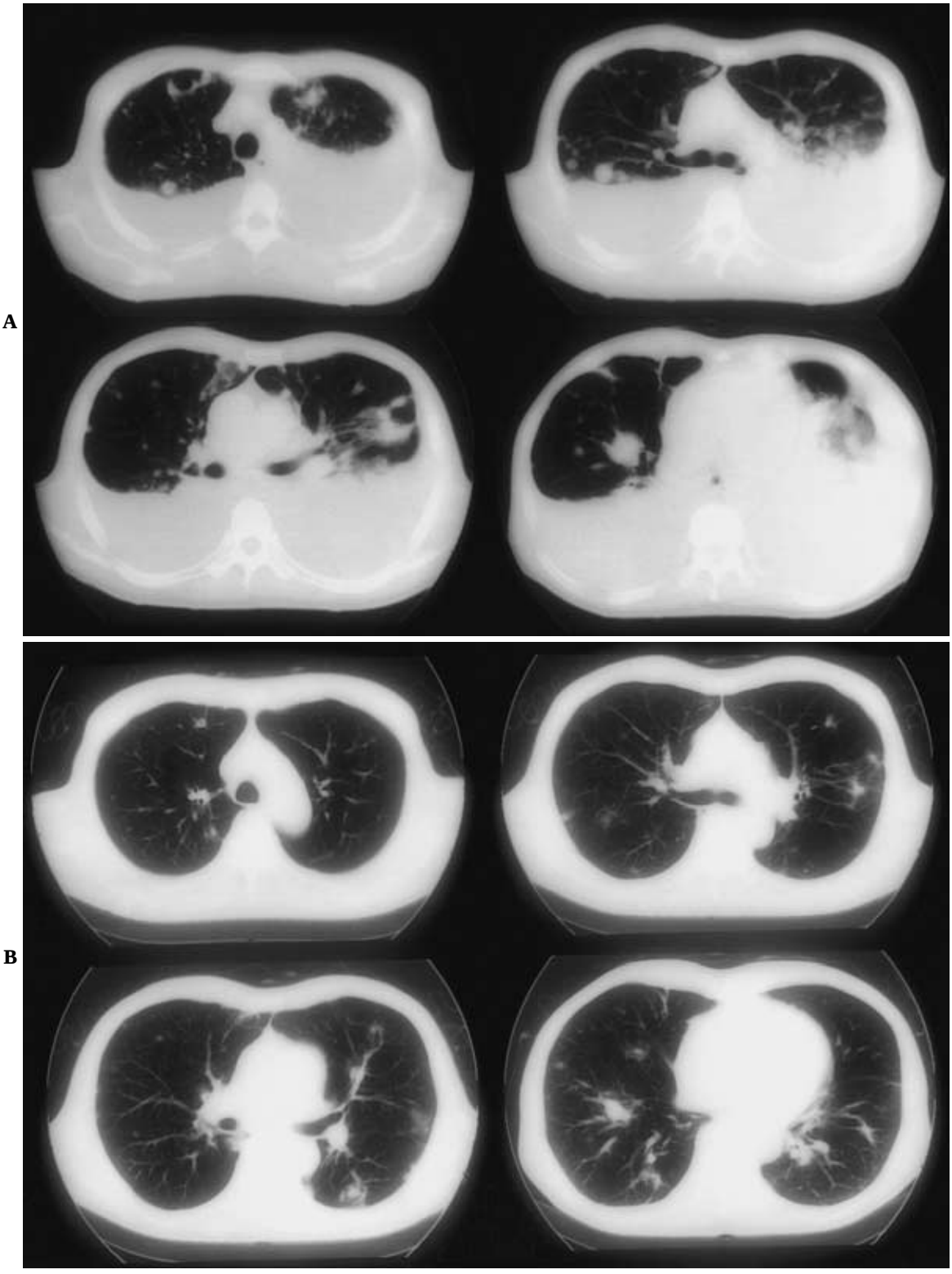

Figure 2. **A.** Chest computed tomography on admission, showing bilateral nodules and pleural effusion. **B.** Chest computed tomography scan 1 month after chemotherapy, showing a decrease in nodules and effusion.

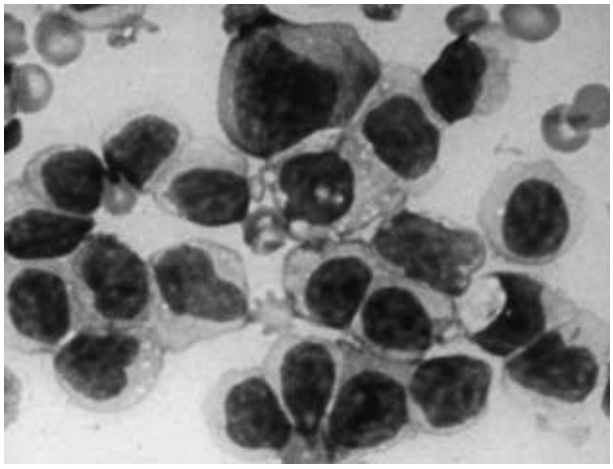

Figure 3. Atypical lymphocytes in pleural fluid.

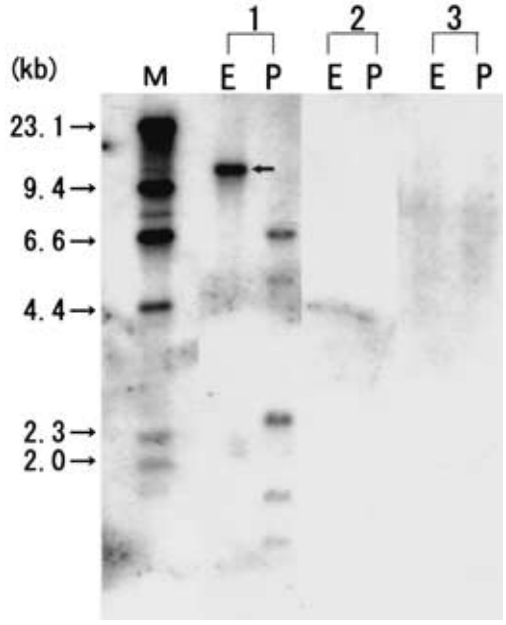

Figure 4. Southern analysis of the cells did not reveal monoclonal integration of the pro-virus HTLV-1. The positive control revealed the band having integration of pro-virus HTLV-1 (arrow). Size marker (M). Positive control (No. 1). Negative control (No. 2). The present patient (No. 3). E, sample digested with Eco RI; P, sample digested with PstI.

Table 2. Flow Cytometoric Analysis of Cells in Pleural Fluid

CD2	98.90%
CD3	83.30%
CD4	78.80%
CD5	83.20%
CD7	78.50%
CD8	13.30%
CD10	0.98%
CD19	11.30%
CD25	4.94%
TCR $\alpha\ \beta$	84.50%
TCR $\gamma\ \delta$	0.30%

VECP therapy (consisting of 1 mg/m^2 of vincristine, 350 mg/m^2 of cyclophosphamide, 40 mg/m^2 of adriamycin, and 40 mg/m^2 of prednisolone on day 1; 30 mg/m^2 of adriamycin, 60 mg/m^2 of ranimustine, and 40 mg/m^2 of prednisolone on day 8; 2.4 mg/m^2 of vindesine, and 100 mg/m^2 of carboplatin on day 15; 100 mg/m^2 of etoposide, and 40 mg/m^2 of prednisolone on days 15-17). After a second course of chemotherapy, disappearance of the pleural effusion, and decrease in size and number of tumors in the lungs was revealed by chest radiography and CT (Figures, 1B and 2B). After six cycles, since chest radiography, CT and other examinations revealed no abnormalities, the patient was diagnosed as being in complete remission.

DISCUSSION

This patient was suspected to have tubercular pleuritis

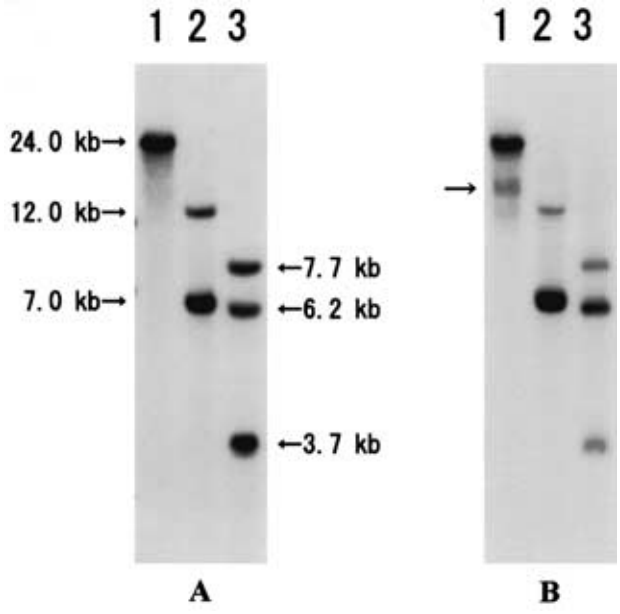

Figure 5. Southern blot analysis of cells in pleural fluid revealed rearrangement of the TCR-β gene (arrow). Genomic DNA of lymphocytes was digested with Bam HI (lane 1), Eco RV (lane 2) and Hind III (lane 3). Negative control (**A**). The present patient (**B**).

because of the high lymphocyte count and elevated ADA in the pleural effusion. These findings are seen with both tubercular pleuritis and lymphoma. Lee et al[8] reported the analysis of 106 lymphocytic pleural fluid samples in which the diagnostic cutoff ADA concentration for tuberculosis was set at 40 U/*l*. ADA concentrations in nontubercular lymphocytic effusions seldom exceeded this cutoff; the ADA concentration ＞40 U/*l* in only three cases (2.8%): two lymphomas and one complicated parapneumonic effusion. In the present case, the ADA concentration was 150 U/*l*, much higher than the usual lymphoma level, and possibly caused by T-cell proliferation.[9]

Although the pleural effusion had been examined by cytology several times at the local hospital, lymphoma was not diagnosed because of the inexperience of the screener. In cases of suspected peripheral lymphoma, cytologic examination should be referred to an expert.

The diagnosis of primary pulmonary lymphoma was defined by Saltzstein[10]; it must originally involve only the lung, or the lung and its regional lymph nodes, and there can be no evidence of dissemination of the tumor for at least 3 months after the diagnosis is established. Our case met these criteria. Koss et al[11] further established the pathologic and clinical criteria to identify primary pulmonary lymphoid lesions as follows: the lesion involved only lung or lung and regional lymph nodes; no lesions extended into the lung from the mediastinum; the patient had no previous history of lymphoma and no clinical or pathologic evidence of tumor outside the thorax at the time of diagnosis of the pulmonary lesion; and no evidence of Hodgkin's disease, lymphomatoid granulomatosis, or lymphoid interstitial pneumonitis. In addition, only open biopsy or lobectomy was accepted for diagnosis. In the present case, the diagnosis of T-cell lymphoma of the lung was made based on Saltzstein's definition and by cytologic examination and gene rearrangement of cells obtained from the pleural effusion. Other cases of lymphoma of the lung have been diagnosed from gene analysis of cells in the pleural effusion when it was not possible to obtain open lung biopsy specimens.[12]

Among peripheral T-cell lymphomas, the unspecified group (PTCL-US) constitutes the most common subtype.[13] Although an adequate tissue sample was not obtained, this case was classified PTCL-US because lymphocyte morphology was variable, comprising medium to large cells expressing variable pan T-cell markers. This subtype tends to occur in older patients at an advanced stage, and overall and failure free survival is poor. For these patients, treatment with CHOP chemotherapy is only minimally effective.[14] Nevertheless, this patient was treated with six cycles of VCAP/AMP/VECP therapy, and has shown complete remission over one year.

On admission to our hospital, the patient was initially suspected to have ATL because of the positive HTLV-1 antibody; however Southern analysis of the cells did not reveal monoclonal integration of the pro-virus HTLV-1, which ruled out the possibility of ATL. This is the first report of peripheral T-cell lymphoma of the lung in an HTLV-1 carrier.

REFERENCES

1. Berkman N, Breuer R, Kramer MR, et al. Pulmonary involvement in lymphoma. *Leuk Lymphoma*. 1996;20:229-237.
2. Papaioannou NA, Watson WL. Primary lymphoma of the lung. An appraisal of it's natural history and a comparison with other localized lymphomas. *J Thorac Cardiovasc Surg*. 1965;49:373-387.
3. L'Hoste RJ Jr, Filippa DA, Lieberman PH, et al. Primary pulmonary lymphomas. A clinicopathologic analysis of 36 cases. *Cancer*. 1984;54:1397-1406.
4. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer*. 1972;29:252-260.
5. Li G, Hansmann ML, Zwingers T, et al. Primary lymphomas of the lung: morphological, immunohistochemical and clinical features. *Histopathology*. 1990;16:519-531.
6. Blattner WA. *Human Retrovirology: HTLV*. New York: Raven Press; 1990:25-65.
7. Tajima K, Cartier L. Epidemiological features of HTLV-1 and adult T cell leukemia. *Intervirology*. 1995;38:238-246.
8. Lee YC, Rogers JT, Rodriguez RM, et al. Adenosine deaminase levels in nontuberculous lymphocytic pleural effusions. *Chest*. 2001;120:356-361.
9. Baganha MF, Pego A, Lima MA, et al. Serum and pleural adenosine deaminase. Correlation with lymphocytic populations. *Chest*. 1990;97:605-610.
10. Saltzstein SL. Pulmonary malignant lymphomas and pseudolymphomas: Classification, therapy, and prognosis. *Cancer*. 1963;16:928-955.
11. Koss MN, Hochholzer L, Nichols BW, et al. Primary non-Hodgkin's lymphoma and pseudolymphoma of lung. *Hum Pathol*. 1983;14:1024-1038.
12. Hanawa T, Chiba W, Fujimoto T, et al. T cell lymphoma presenting as recurrent bilateral pulmonary infiltrates over five years. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1996;34:363-368 (in Japanese; abstract in English).
13. Lopez-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell Lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. *Ann Oncol*. 1998;9:

849-855.
14. Savage KJ, Chhanabhai M, Gascoyne RD, et al. Characterization of peripheral T-cell lymphomas in a single North American institution by WHO classification. *Ann Oncol*. 2004;15:1467-1475.