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ORIGINAL ARTICLE

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See end of article for authors' affiliations

Correspondence to: Dr Sun Wook Kim, Research Institute and Hospital, National Cancer Center, Madu-dong 809, Ilsandong-gu, Goyang, Gyeonggi, 410-769, Korea; swkim@ncc.re.kr

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Background: The epidermal growth factor receptor (EGFR) has been reported to be overexpressed in anaplastic thyroid carcinoma (ATC). In vitro studies have shown that EGFR tyrosine kinase inhibitors (TKIs) greatly inhibit cellular growth and induced apoptosis in the ATC cell lines, while somatic mutations in the tyrosine kinase domain or an increased gene copy number are associated with increased sensitivity to TKIs in non-small cell lung cancer.
Aim: To investigate the prevalence of EGFR overexpression, gene amplification and activating mutation in the tyrosine kinase domain in patients with ATC.
Methods: The *EGFR* gene status and protein expression were investigated by direct DNA sequencing of the hot-spot regions in exons 18, 19 and 21, fluorescence in situ hybridisation (FISH), and immunohistochemistry in tumour tissues from 23 patients with ATC.
Results: On mutational analysis and FISH, neither mutations in the hot-spots nor gene amplification was observed. However, high polysomy was identified in 14/23 (60.9%) patients with ATC. All cases with immunohistochemistry (IHC) positivity (n = 6) had high polysomy, whereas 8/17 (47.1%) cases with IHC negativity had high polysomy (p = 0.048). High polysomy was observed in all 10 cases with giant cell subtype, but in only 4/11 (36.3%) with squamoid and 0/2 with spindle cell sarcomatoid subtype. There was no statistically significant correlation between FISH positivity of ATC tumour and presence of well-differentiated component.
Conclusion: Despite the low incidence of somatic *EGFR* gene mutation and amplification in the study samples, in view of the fact that high polysomy was often identified by FISH, as well as the current lack of therapeutic options, EGFR TKIs are worth investigating for treating the patients with ATC who have at least giant cell subtype.

Anaplastic thyroid carcinoma (ATC) is a rarely encountered tumour, but is one of the most aggressive malignancies.[1] Most patients with ATC have an extremely poor prognosis,[2] which reflects the current lack of curative therapeutic options and also the need for developing novel therapeutic strategies. Fortunately, the recent advance of molecular-targeted therapy has introduced several new therapeutic strategies against epidermal growth factor receptor (EGFR), which has been reported to be overexpressed in ATC.[3–5] These drugs included the small-molecule tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib, and the monoclonal antibodies such as cetuximab that are directed at the receptor. Of particular interest, the specific *EGFR* gene mutations that are clustered within the tyrosine kinase domain were recently reported to be associated with the sensitivity of small molecule TKIs.[6–8] Furthermore, a high *EGFR* gene copy number, including gene amplification and high polysomy, has been shown to be significantly associated with a better response and improved survival for non-small cell lung cancer (NSCLC).[9 10] Therefore, as indicators for the effectiveness of TKIs, the mutational status of the tyrosine kinase domain and a high gene copy number of the *EGFR* gene in different primary cancers may have important clinical consequences, although there are still numerous questions to be answered concerning the relevant biological parameters.

Based on these current results, we analysed the mutational status of the tyrosine kinase domain and the gene copy number of the *EGFR* gene in ATC tissues to infer whether TKIs may have anti-tumour activity against ATC; if so, this would provide a rationale for clinical trials with TKIs.

MATERIALS AND METHODS

Tissue samples and pathology

We retrieved tumour tissue samples from 23 patients with ATC from the archives of the Departments of Pathology at Seoul National University Hospital, Seoul, Korea and at the National Cancer Center, Goyang, Korea. The pathological diagnosis was made by three professional pathologists (GKL, SYP and SHP) according to the World Health Organization classification; the representativeness of the samples was reconfirmed from the H&E stained slides by GKL. The patients' ages ranged from 52 to 80 years with a median age of 63 years. There were 7 men and 16 women. The subtypes of ATC were as follows: 11 squamoid; 7 giant cell; 2 spindle cell sarcomatoid; and 3 mixed giant and spindle cell sarcomatoid. Of note, 13/23 (56.5%) cases contained a well-differentiated component. There was no paucicellular variant.

Immunohistochemistry

Expression of EGFR was determined by means of immunohistochemistry (IHC) using the mouse anti-human EGFR (clone

Abbreviations: ATC, anaplastic thyroid carcinoma; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

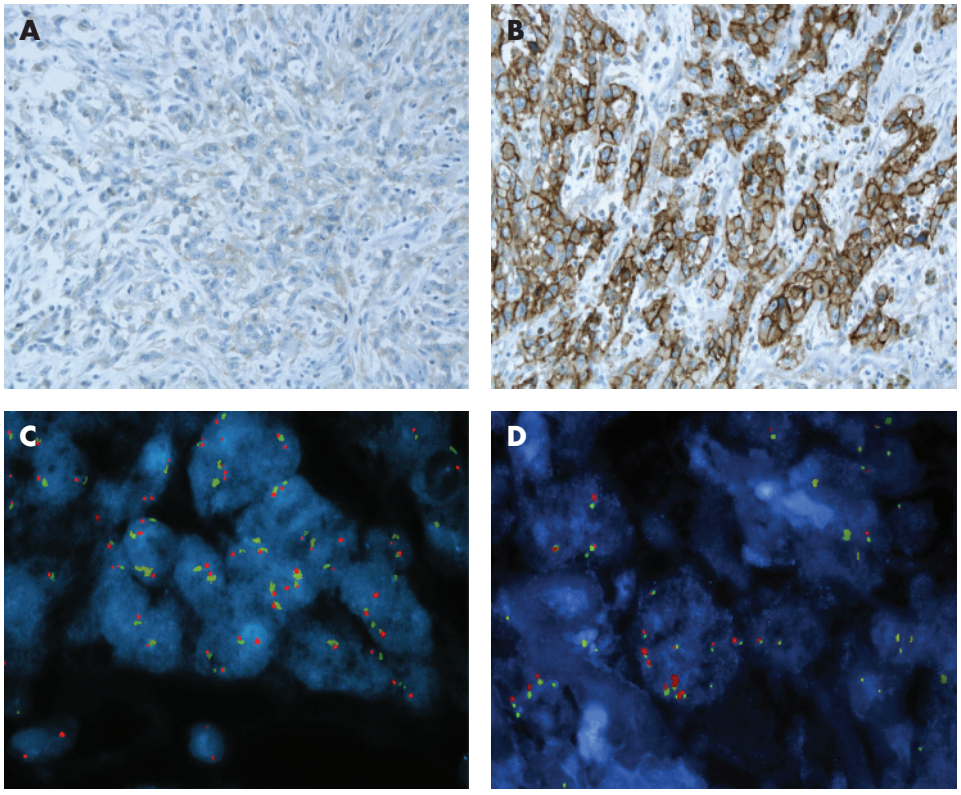

Figure 1 Expression of EGFR protein on immunohistochemical (IHC) analysis (A and B) and fluorescence in situ hybridisation (FISH) analysis of the number of gene copes (C and D). No tumour staining was scored as IHC negative (A), and moderate to strong membranous staining was scored as IHC positive (B). FISH of the diploid tumour cells showed one or two red signals (EGFR), and one or two green (CEP7) signals in most cells (panel C), whereas cells with high polysomy showed four or more red and green signals in more than 40% of cells (panel D).

H11 monoclonal antibody; DakoCytomation, Carpinteria, California, USA). Evaluation was done according to the proportion of reactive cells within the tumours. The proportion score described the estimated fraction of positively stained tumour cells (0, no visible reaction; 1, <10%; 2, 10–50%; 3, 50–100% of the tumour cells were stained). When >10% of tumour cells showed membranous staining of any intensity (score 2 or 3), the tumour was considered positive for EGFR.

Fluorescence in situ hybridisation

Fluorescence in situ hybridisation (FISH) studies were performed using the LSI EGFR SpectrumOrange/CEP7 Spectrum Green probe (Vysis, Abbott Laboratories, Abbott Park, Illinois, USA). We analysed 50 non-overlapping tumour cell nuclei for the observed number of red (*EGFR*) and green (*CEP7*) signals. We determined the number of gene copies of the *EGFR* gene and we classified them according to the six FISH categories defined by Cappuzzo *et al*.[9] Those tumours with a high degree of polysomy or amplification were considered to be FISH positive.

Detection of hot-spot mutation for EGFR gene

The two 10 μm tissue sections that were taken from the paraffin-embedded tumour specimens were incubated at 60℃ for 1 hour, deparaffinised by washing in xylene, and dehydrated in 100%, 95% and 80% solutions of ethanol. The tumour specimen was then scraped from the slide for performing DNA isolation; the genomic DNA was extracted using a Purgene Kit (Gentra, Minneapolis, Minnesota, USA) according to the manufacturer's instructions. PCR was performed using 5 μl of the genomic DNA extract, 1U Taq polymerase, 0.25 mM of each dNTP, 10 mM Tris-HCl, 40 mM KCl, 1.5 mM $MgCl_2$ and

Table 1 *EGFR* gene status in anaplastic thyroid carcinoma

	FISH (−)				FISH (+)		
	Disomy	Low trisomy	High trisomy	Low polysomy	High polysomy	Gene amplification	Total
IHC (+)	0	0	0	0	6	0	6
IHC (−)	0	2	0	7	8	0	17
Total	0	2	0	7	14	0	23

FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry.
FISH positive: high polysomy (≥4 copies in ≥40% of cells) or gene amplification (defined as the presence of tight *EGFR* gene clusters and a ratio of the *EGFR* gene to the chromosome of ≥2 or ≥15 copies of the *EGFR* gene per cell in ≥10% of the analysed cells).
FISH negative: disomy (≤2 copies in >90% of cells), low trisomy (≤2 copies in ≥40% of cells, 3 copies in 10–40% of the cells, ≥4 copies in <10% of cells), or low polysomy (≥4 copies in 10–40% of cells). IHC positivity was defined as more than 10% of tumour cells showing membranous staining of any intensity.

20 pmol of the primers in a final volume of 20 µl. The PCR conditions were 95℃ for 5 min, 95℃ for 30 s, 55℃ for ×30 s, 72℃ for 30 s for 40 cycles, and then 72℃ for 10 min. All PCR procedures were repeated twice. The EGFR mutations that are sensitive to TKIs in NSCLC have been reported within exons 18, 19, and 21. Therefore, exons 18, 19, and 21 of the *EGFR* gene were amplified using PCR assays with the following primers: exon 18, GACCCTTGTCTCTGTGTTCTTGT (forward), TATACAG CTTGCAAGGACGG (reverse outside) and CCAGACCATGAGA GGCCCTG (reverse inside); exon 19, CACAATTGCCAGTTAA CGTCTTC (forward), AGGGTCTAGAGCAGAGCAGC (reverse outside) and GCCTGAGGTTCAGAGCCAT (reverse inside); exon 21, CATGATGATCTCTCCCTCACAG (forward), CTGGTCCCTGG TGTCAGGAA (reverse outside) and GCTGGCTGACCTAAAGC CACC (reverse inside). After purification of the PCR products, direct DNA sequencing was performed using the MegaBACE DNA Analysis System (Amersham Biosciences, Sunnyvale, California, USA) as the standard protocol.

Statistical analysis

Statistical analysis was performed using Fisher's exact test; $p<0.05$ was considered statistically significant.

RESULTS

IHC and FISH analyses were available in 23 ATC cases (table 1 and fig 1). We found neither EGFR kinase domain mutations nor gene amplification. We observed 6/23 patients (26.1%) with IHC positivity and 14/23 (60.9%) with high polysomy or FISH positivity. All 6 IHC positive cases were found to be FISH positive (100.0%), while 8/17 IHC negative cases were FISH positive (47.1%). However, 6/14 (42.9%) FISH positive cases showed IHC positivity, while 0/9 FISH negative cases showed IHC positivity. There was a statistically significant correlation between FISH positivity and IHC positivity ($p = 0.048$). By subtype of ATC, all 10 cases with giant cell only or mixed giant cell and spindle cell sarcomatoid subtype showed high polysomy, while 4/11 (36.3%) cases with squamoid and no cases with spindle cell sarcomatoid showed high polysomy (table 2). The frequency of high polysomy or FISH positive in ATC patients with a well-differentiated component and in those without was not statistically different (8/13 (61.5%) vs 6/10 (60.0%), $p = 1.0$). When the FISH status of both the ATC tumour component and the well-differentiated component was examined in 4/11 cases having both components, two cases were FISH positive in the ATC tumour but FISH negative in the well-differentiated component, while the other two were FISH negative in both the ATC component and the well-differentiated component.

DISCUSSION

Recently, the newer molecular targeted therapies have entered or are rapidly entering into clinical practice. In particular, such EGFR inhibitors as gefitinib or erlotinib have been reported to produce an objective tumour response and/or survival benefit for patients with NSCLC.[11–13] Furthermore, specific mutations in the tyrosine kinase domain and a high gene copy number of the *EGFR* gene have been shown to be significantly associated with EGFR TKI sensitivity and an objective tumour response.[7–10] In the current study, we found neither gene mutations in the *EGFR* hot-spot regions nor gene amplification in the ATC specimens, but we observed a high frequency of high polysomy in 14/23 (60.9%) patients. Of note, FISH positivity or increase in EGFR gene copy number was more frequently found in the specimens with EGFR overexpression, and there was a statistically significant association between FISH status and IHC status, suggesting that high polysomy might be one of the underlying genetic mechanism of EGFR overexpression in ATC. Of greater interest, we observed a high frequency of high polysomy in a particular subtype, ie giant cell histology (giant cell subtype and mixed giant cell and spindle cell sarcomatoid subtype). Whether ATC had a well-differentiated component did not correlate with FISH positivity. Although only a small number of specimens were analysed, we could not identify gene amplification or high polysomy in a well-differentiated component; however, corresponding ATC tumour cells showed high polysomy. In addition, we also could not identify any gene mutation, amplification or high polysomy in four poorly differentiated carcinomas (data not shown). Those findings might help to explain or shed some light on the tumourigenesis of ATC.

Aberrantly activated EGFR receptors contribute to many stages of the malignant process, and the recent discovery of tyrosine kinase domain activating mutations is very important in this respect.[14] However, EGFR gene amplification has also been described in many tumours, such as central nervous system tumours,[15 16] gastric cancer[17] and breast cancers.[18 19] Furthermore, high polysomy has been reported recently to play a role in overexpression of EGFR in NSCLC and of HER2 in breast cancer.[20 21] For NSCLC, the patients with a high gene copy number such as gene amplification or high polysomy had a better response to EGFR TKIs,[9 10] while there was no association between a high gene copy number and the responsiveness to EGFR TKIs in glioblastomas.[22] Therefore,

Table 2 *EGFR* gene status in anaplastic thyroid carcinoma according to histological subtype

			IHC		FISH	
Subtype histology	Presence of WD component		+ (n = 6)	− (n = 17)	+ (n = 14)	− (n = 9)
Squamoid (n = 11)	Yes	8	2	6	4	4
	No	3	0	3	0	3
			2	9	4	7
Giant cell (n = 7)	Yes	3	2	1	3	0
	No	4	1	3	4	0
			3	4	7	0
Spindle cell (n = 2)	Yes	1	0	1	0	1
	No	1	0	1	0	1
			0	2	0	2
Mixed giant cell/ spindle cell (n = 3)	Yes	1	0	1	1	0
	No	2	1	1	2	0
			1	2	3	0

WD, well-differentiated.

Take-home messages

- Epidermal growth factor receptor (EGFR) status in anaplastic thyroid carcinoma (ATC) will help to explain the tumourigenesis of ATC and to provide the rationale for use of EGFR tyrosine kinase inhibitors in treatment of this tumour.
- Neither gene mutations in the activating domain nor gene amplification of EGFR were found, but high polysomy was frequently observed in ATC, especially in the giant cell histological subtype.
- There was no correlation between FISH positivity of the ATC tumour and presence of a well-differentiated component.

whether a high number of gene copies is associated with responsiveness to EGFR TKIs in different primary cancers should be addressed. In addition, the responsiveness to EGFR TKIs between the patients with gene amplification and those with high polysomy should also be evaluated in further studies.

We should be cautious in interpreting the results of our study because only 23 cases were analysed, which is a relatively small sample. The recent study of the EGFR amplicon which investigated whether amplified DNAs were specific to EGFR or just represented polysomy of chromosome 7 has shown that EGFR gene copy number gain may occur by amplification of a discrete genomic region or by gains of the short arm of chromosome 7 with a breakpoint near the EGFR gene locus.[19 23] Gene amplification leading to EGFR overexpression is often found in human cancers. Therefore, as the frequency of EGFR overexpression is lower than that of high polysomy, another locus segregating with EGFR gene can be more relevant. Furthermore, although in vitro studies have shown that gefitinib greatly inhibited cellular proliferation and induced apoptosis in the ATC cell lines, and also slowed tumour growth in a nude mouse model,[4 5] it is difficult to predict in vivo whether patients with ATC, especially those who exhibit high polysomy without any mutation or gene amplification, will benefit from EGFR TKIs.

In conclusion, although we were not able to identify *EGFR* gene mutations in hot-spot regions or gene amplifications, we found an increased *EGFR* gene copy number in 60.9% of patients with ATC, especially in those with giant cell subtype. In addition, it should be remembered that there are few treatment options for patients with advanced ATC, especially for those in whom surgery, radiotherapy and/or chemotherapy have been unsuccessful. Therefore, further clinical investigations using EGFR TKIs for treating this type of tumour are warranted.

Authors' affiliations
D H Lee, G K Lee, S-y Kong, M C Kook, S K Yang, S W Kim, K-W Chung, E S Lee, S W Kim, Research Institute and Hospital, National Cancer Center, Goyang, Gyeonggi, Korea
S Y Park, S H Park, Department of Pathology, Seoul National University College of Medicine, Seoul, Korea
B Keam, D J Park, B Y Cho, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

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Figure 1 Sessile polypoidal friable carinal tumour with tumourous occlusion of both the main bronchi. Note collapsed left lung and hyperinflated right lung. Inset: smooth right bronchial mucosa after scooping out the tumour fragment.

was sudden respiratory distress and the child died.

Autopsy revealed a 2×1.8×1.7 cm, sessile, polypoidal, soft, whitish-yellow exceedingly friable tumour in the carina and left main bronchus (fig 1). The left lung was collapsed, firm with a dark brown cut surface. An unattached friable piece of tumour (0.9×0.4 cm) was present in the lumen of the right main bronchus. Removal of the right bronchial luminal fragment revealed smooth and glistening underlying mucosa (fig 1, inset). The right lung was voluminous, oedematous and haemorrhagic. On histology, a benign spindle cell tumour, arranged in intersecting fascicles, was seen to originate from the carinal smooth muscles (fig 2). The cells were stained red by Masson trichrome stain, with a strong immunoreactivity for smooth muscle actin, and were non-reactive to EBV antigen (EBNA) and CD117. No tumour was seen elsewhere.

Predisposing factors for bronchopulmonary leiomyomata in adults have not been well documented. In sharp contrast, in children, immunodeficient states have served as fertile grounds for benign and malignant smooth muscle proliferations.[2] Chadwick *et al*[3] first described pulmonary leiomyoma in three HIV-positive children; prior to their report, only eight children with such tumours had been reported.[3] Since then, 18 cases have been described with HIV infection and other immunodeficient states.[2 4] Ours will be the 19th patient. The role of EBV in smooth muscle tumourigenesis in immunocompromised conditions has been proved beyond doubt.[2 4] In the reported case, the HIV status was not available. There were no features suggesting primary or acquired immunodeficiency. Immunohistochemistry was negative for EBV antigens. In an attempt to delineate the histogenesis, we used an immunostain for CD117, as the tracheo-bronchial tree is a foregut derivative. However, this was non-reactive. Benign endobronchial or parenchymal leiomyomata have always been described as ''firm'' or ''hard''. Surprisingly, this tumour was extremely friable. A fragment had broken off from the main mass to occlude the right bronchus, which precipitated the fatal respiratory distress. Such a phenomenon, though not previously reported, should be borne in mind when diagnostic bronchoscopy is attempted. The tumours are amenable to surgical or endoscopic intervention. It is important to assess the HIV and EBV status when tumours are multifocal or involve extra-pulmonary sites.

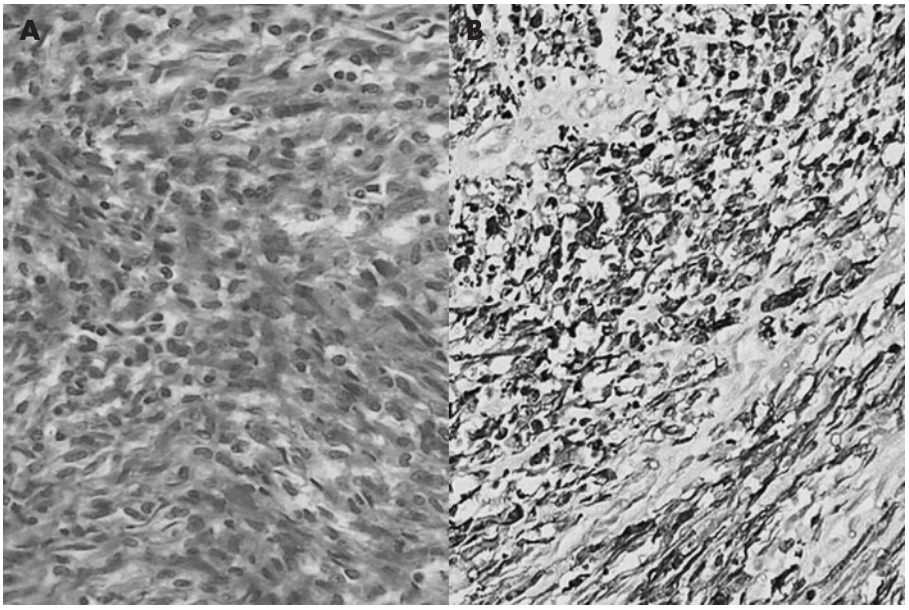

Figure 2 (A) Interlacing bundles of spindle-shaped cells without pleomorphism or mitoses (H&E, ×400). (B) Strong positivity with smooth muscle actin (×400).

Ruta Goregaonkar
Department of Pathology, Tata Memorial Hospital, Mumbai, India

Pradeep Vaideeswar, Shobhana P Pandit
Department of Pathology (Cardiovascular & Thoracic Division), Seth G S Medical College, Mumbai, India

Correspondence to: Dr Pradeep Vaideeswar, Department of Pathology (Cardiovascular & Thoracic Division), Seth G S Medical College, Parel, Mumbai 400 012, India; shreeprajai@yahoo.co.in

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CORRECTIONS

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There was an error in an author name in the July issue of the journal (Smellie WSA, Hampton KK, Bowlees R, *et al*. Best practice in primary care pathology: review 8. *J Clin Pathol* 2007;**60**:740–8.) The correct name of the third author is R Bowley.

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There was an omission in an article published in the August issue of the journal (Lee DH, Lee GK, Kong S-Y, *et al*. Epidermal growth factor receptor status in anaplastic thyroid carcinoma. *J Clin Pathol* 2007;**60**:881–4.) The following statement should have been included: DHL and GKL contributed equally to this work.