anterior leaflet of the mitral valve upstream of the aneurysm.

After excision of the obstructing fibromuscular mem-
brane and a standard septal myectomy, the aneurysm
was plicated using pledgeted horizontal mattress sutures
of 4-0 Prolene (Ethicon, Somerville, NJ). The sutures
were placed through the right atrium and through the
interatrial septum at the lower margin of the aneurysm
into the LVOT, picking up multiple bites through the sac
of the aneurysm, and was passed back into the right
atrium through the superior margin of the aneurysm.
This allowed the pledgets to be seated in the right atrium
to minimize pledget load and scarring in the LVOT
(Fig 2B).

A postrepair transesophageal echocardiogram
demonstrated laminar flow across a normal-appearing
LVOT and no residual aneurysm. Both the aortic and
mitral valves were competent (Fig 3). The patient had
an uneventful recovery, was discharged home 5 days
postoperatively, and continues to do well without
any residual hemodynamic lesions at 6-month
follow-up.

Comment

Aneurysms of the aortomitral curtain or the intervalvular
fibrosa are rare and have only been described previously
in association with infective endocarditis [1, 2]. To our
knowledge, this is the first description of congenital
aneurysm of aortomitral intervalvular fibrosa.

Our patient had undergone a ventricular septal defect
and aortic coarctation repair in the past. On retrospective
review of the patient’s imaging studies before the pro-
cedure, a smaller dilatation was noted in the region of the
aortomitral intervalvular fibrosa, which subsequently
progressed to its current size. Although pseudoaneur-
ysms of the LVOT have been reported with injury to the
area from surgical procedures [3], it was unlikely in this
patient, because the findings preceded the first surgical
intervention.

Because these aneurysms per se were asymptomatic,
clinical detection of this pathologic process depended on
the presence of other associated symptomatic lesions.
Although the natural history of such lesions is not well
known, surgical repair of aortomitral intervalvular fibrosa
is justified based on the progressive enlargement of the
aneurysm, as seen in our case.

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Histologic Evolution From
Adenocarcinoma to Squamous
Cell Carcinoma After Gefitinib
Treatment

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We report two cases of lung cancer with histologic
transformation from adenocarcinoma to squamous cell
carcinoma after gefitinib treatment. Both cases involved
advanced lung cancers, initially confirmed as adenocar-
cinomas with sensitive epidermal growth factor gene
mutations. After gefitinib treatment, the second patho-
logic examination in each case revealed squamous cell
carcinoma retaining identical mutations without newly
acquired resistance mutations. The underlying mecha-
nism may have been pluripotent tumor cells with diver-
gent differentiation or mixed lung cancer including both
adenocarcinomatous and squamous cell carcinomatous
components. This report widens the spectrum of histo-
logic evolution as a mechanism underlying the acquisi-
tion of drug resistance.

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Gefitinib and erlotinib, selective tyrosine kinase in-
hibitors (TKI) of epidermal growth factor receptor
(EGFR), have demonstrated effectiveness against adeno-
carcinomas with EGFR mutation. Herein, we report two
cases of biopsy–confirmed lung adenocarcinomas that
underwent histologic evolution to squamous cell carci-
noma (SCC) after gefitinib treatment.

Case Reports

Case 1

A 51-year-old woman presented with symptoms of
coughing and a loss in body weight of 7 to 8 kg during a
period of 3 to 4 months. Roentgenogram and computed
tomography scans revealed a mass greater than 8 cm
in the right lung (Fig 1A) accompanied by multiple
pleural nodules. Video-assisted thoracoscopic surgery
confirmed pleural metastasis, and pathologic examina-
tion revealed a metastatic adenocarcinoma with intra-
cytoplasmic mucin and glandular structures (Fig 1B).
Immunohistochemical analysis confirmed primary lung

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adenocarcinoma, on the basis of immunoreactivity of the tumor cells to thyroid transcription factor-1 and napsin A and negative staining for p40 or CK5/6. Mutation analysis for the EGFR gene revealed deletion E746–A750 in exon 19. Gefitinib was administered, and the patient presented a good initial response, manifest as a rapid decrease in tumor size. Four months later, the patient underwent a right lower lobe lobectomy and mediastinal lymph node dissection by means of video-assisted thoracoscopic surgery. We found a 2-cm residual tumor comprising exclusively squamous cells (Fig 1C), which was immunoreactive to p40 and CK5/6, and stained negatively for thyroid transcription factor-1 or napsin A. Repeated EGFR mutation analysis showed the identical EGFR gene mutation as deletion E746–A750 in exon 19 without newly acquired resistance mutations. Immunostaining for anti-EGFR E746–A750 del antibodies (clone SP111, Ventana Medical Systems, Inc, Tucson, AZ) confirmed the SCC did express mutated EGFR protein (Fig 1D). Six months later, computed tomography revealed a recurrent tumor in the right upper lobe adjacent to the previous suture line. The tumor was removed by video-assisted thoracoscopic surgery segmentectomy, and pathologic examination still revealed only SCC. Chemotherapy (gemcitabine and cisplatin) was initiated, and the patient is currently receiving regular follow-up.

Case 2
A 61-year-old nonsmoking woman presented with coughing for a period of 3 months. Computed tomography scan disclosed a tumor in the right upper lobe measuring 6.9 cm (Fig 2A). A loculated pleural effusion on the right side and multiple tiny nodules in bilateral lungs were also found. Bronchoscopic biopsy confirmed a thyroid transcription factor-1(+) p40(–) lung adenocarcinoma (Fig 2B) carrying a sensitive EGFR mutation (exon 21 point mutation 2573T>G, L858R). The tumor size decreased slightly with gefitinib treatment but was enlarged 1 year later. Six cycles of pemetrexed plus platinum chemotherapy were administered, and the main tumor remained stationary in size with persistent right pleural effusion. Six months later, a soft tissue mass was found in the right pleura by sonography, and a biopsy revealed SCC (Fig 2C) carrying the identical EGFR mutation (exon 21 point mutation, 2573T>G, L858R) with no secondary mutations. Immunostaining for anti-EGFR L858R antibodies (clone SP125, Ventana) confirmed the presence of mutant EGFR protein in SCC (Fig 2D). Erlotinib was administered; however, the patient passed away as a result of Klebsiella pneumonia.

Comment
The TKIs, gefitinib and erlotinib, are widely used as first-line therapy in selected patients with advanced nonsmall cell lung cancers (NSCLCs) carrying sensitive EGFR mutations. Sensitive mutations including deletion in exon 19 and L858R in exon 21 tend to be more common among women, East Asians, light smokers, and patients with adenocarcinomas [1]. Despite an initial, positive response to TKIs, most patients with NSCLCs eventually undergo disease progression within a median interval of 12 months [2, 3]. The mechanisms underlying drug resistance include secondary EGFR mutation or alternative pathways. Secondary EGFR T790M mutation in exon 20 and c-MET amplification are the two most common newly acquired drug-resistant genomic changes [2, 4, 5]. These tumors maintain their original EGFR mutation [2, 4]. It is interesting to note that the tumor may undergo histologic...
Sequist and associates [2] observed histologic evolution from adenocarcinoma into small cell lung cancer in 5 patients with NSCLC. This clearly demonstrates that histologic change, as opposed to EGFR mutation, is an alternative mechanism associated with drug resistance.

Here, we reported two cases of histologic evolution from adenocarcinoma to SCC after gefitinib treatment. Reports of this nature were not reported in the study by Sequist and colleagues [2]. In the first case, SCC was the only residual component after TKI treatment and also the only component in the recurrent tumor obtained in the second operation. In the second case, the tumor initially remained stationary but progressed 1 year later after TKI treatment. The second biopsy at the pleura revealed SCC. In both cases, no newly acquired EGFR mutation such as T790M was observed, and immunohistochemical staining confirmed that their SCCs did express mutated EGFR. Our findings strongly support the assertion that histologic evolution can be a mechanism associated with TKI resistance, and can widen the spectrum of histologic evolution in NSCLCs.

The benefits of TKIs against nonadenocarcinoma NSCLCs harboring sensitive EGFR mutations are less pronounced than those against adenocarcinomas [6]. Shukuya and coworkers [6] conducted a review study testing the efficacy of gefitinib in patients with nonadenocarcinoma NSCLCs carrying sensitive EGFR mutations. Sixteen cases of SCC with sensitive EGFR mutations receiving gefitinib had an average response rate of 38% and a median progression-free survival of 3.1 months, the advantages of which are significantly less pronounced than those against adenocarcinomas harboring sensitive EGFR mutations (response rate, 69%; median progression-free survival, 9.8 months) [6]. Histologic evolution from sensitive adenocarcinoma to a less sensitive type may confer drug resistance in lung cancers.

This study proposes two possible mechanisms to explain this interesting finding. First, the tumor may contain pluripotent tumor stem cells, which undergo divergent differentiation after treatment with TKI. Second, the tumor may be a mixed type lung cancer such as an adenosquamous carcinoma, in which only the squamous cell component remains after TKI treatment. Nonetheless, in both conditions, SCC survives during the course of TKI treatment. This histologic evolution in lung cancer during the course of TKI treatment underscores the importance of a repeat tissue proof when the tumor has acquired drug resistance to refine the treatment policy and chemotherapy regimen. In cases in which the residual or recurrent tumor is resectable, surgical intervention is an effective treatment option to extirpate the surviving tumor line.

References

Pneumonectomy and Contralateral Metastasectomy Through a Single Thoracotomy in a 9-Year-Old Girl With a Giant Tumor

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A 9-year-old girl with a giant tumor of the right lung and an isolated metastasis of the left lower lobe underwent combined pneumonectomy and metastasectomy through means of a right thoracotomy. Her postoperative course was uneventful. The operative approach of a tumor of this scale and the concurrent contralateral metastasectomy are described and discussed.

(Malignant peripheral nerve sheath tumor (MPNST) is a rare, yet one of the most common, non-rhabdomyosarcoma soft tissue sarcomas in the pediatric population. These tumors occur most frequently at axial sites, are characterized by local aggressiveness, and have a tendency to metastasize early [1]. Treatment of MPNST represents a major challenge as there is no reliable modality other than radical surgery. Chemotherapy and radiotherapy are occasionally used in selected patients with unresectable tumors or metastatic disease [2, 3].

A 9-year-old girl underwent surgical excision of an MPNST of the cervical spine at the age of 7 years followed by adjunctive chemotherapy and was free of residual disease thereafter. Six months ago a lesion appeared in the right lung, and biopsy revealed metastasis of the primary tumor. She was advised to receive chemotherapy; however, this approach proved ineffective with the tumor increasing rapidly in size. In addition, a metastasis in the lower lobe of the left lung was detected (Fig 1). She was then referred to our unit for possible surgical treatment.

Fig 1. Schematic representation showing the approach to the left hemithorax. (A, B) A pleural incision is performed in front of the esophagus, through which (C) the left lower lobe is delivered. (IVC = inferior vena cava; RIPV = right inferior pulmonary vein.)