Prolonged Remission of Disseminated Atypical Adenomatous Hyperplasia Under Gefitinib

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Abstract: Atypical adenomatous hyperplasia (AAH) is a putative precursor of bronchioloalveolar carcinoma (BAC) and adenocarcinoma of the lung, developing from terminal respiratory unit cells. AAH and BAC lesions typically present as ground-glass opacities at spiral chest computed tomography. Epidermal growth factor receptor polysomy/mutations, conferring higher sensitivity to Gefitinib, are frequent in BAC but less common in AAH. We describe an interesting case of disseminated AAH showing a sustained remission under Gefitinib therapy.

Key Words: AAH, BAC, Gefitinib, FISH, CT screening.

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CASE REPORT

In September 2001, a 62-year-old female smoker of 76 packs/year, without history of previous cancer or respiratory diseases, was enrolled in a chest computed tomography (CT)-screening trial. In October 2002, the patient underwent right upper lobe lobectomy for stage IA adenocarcinoma. The patient resumed smoking 1 year after surgery. In November 2004, chest CT revealed disseminated bilateral ground-glass opacity (GGO), ranging from 5 to 20 mm (Figure 1*A*). Each CT section was graded separately according to the percentage of the area showing GGO abnormalities. The mean extent of GGO, calculated with the method of visual score, reached 20% in three zones (aortic arch, carina, and 2 cm above the diaphragm) of each lung. Lung function tests showed moderate obstructive lung impairment. Left video-assisted thoracoscopy revealed multiple subcentimetric nodules, involving the whole parenchyma. Excision of one partially solid lesion of 9 mm in the upper lobe showed bronchioloalveolar carcinoma (BAC) at frozen section, and two additional lesions were resected from upper and lower lobes. The final patho-

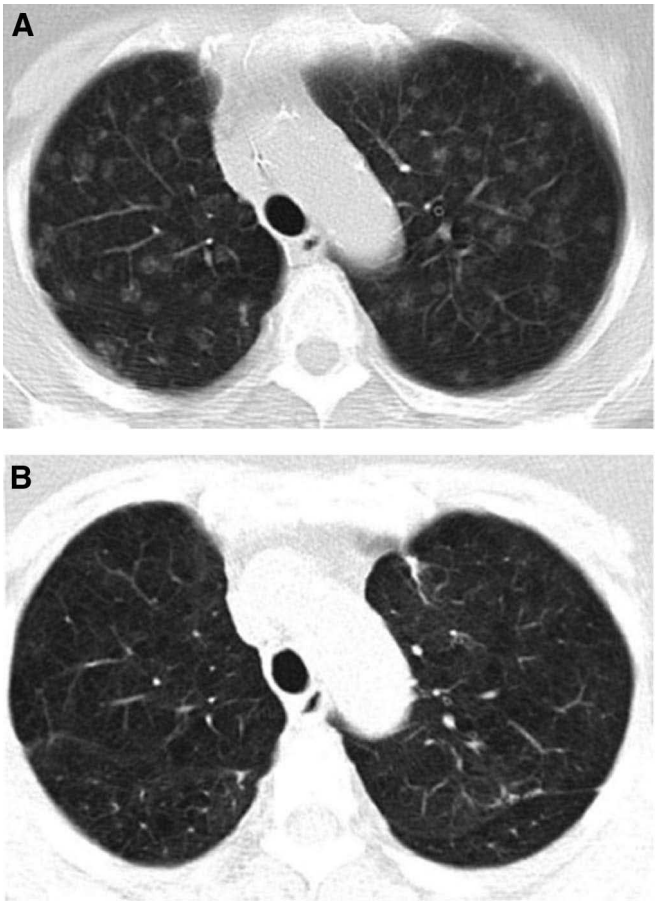

FIGURE 1. *A*, Chest computed tomography as on November 2004 showing disseminated bilateral ground-glass opacity, ranging from 5 to 20 mm. *B*, Chest computed tomography after 12 months of Gefitinib therapy showing complete resolution of ground-glass opacity.

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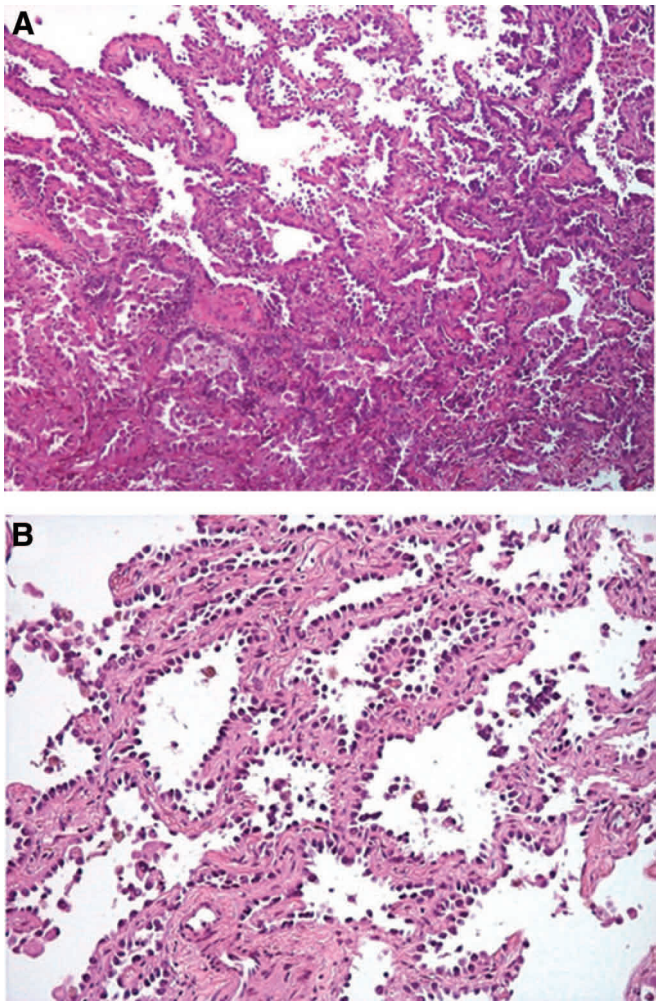

FIGURE 2. *A,* Pathologic features of nonmucinous bronchioloalveolar carcinoma (hematoxylin-eosin stain, ×20). *B,* Atypical adenomatous hyperplasia (hematoxylin-eosin stain, ×20).

logic report confirmed nonmucinous BAC in the first specimen and atypical adenomatous hyperplasia (AAH) in the other two biopsies (Figures 2*A,B*). Molecular analysis of the *epidermal growth factor receptor* (*EGFR*) gene (exons 18–21) showed no mutations in BAC and AAH lesions, but fluorescence in situ hybridization analysis detected high levels of EGFR polysomy (defined when more than two specific signals for both *EGFR* genes and chromosome 7 centromeric probes are present per nucleus) in BAC, and disomy (defined when two copies of both EGFR and chromosome 7 centromeric probes are observed per nucleus) in all AAH specimens

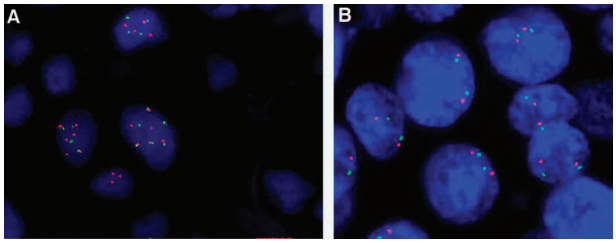

FIGURE 3. *A,* bronchioloalveolar carcinoma specimen with *epidermal growth factor receptor* (*EGFR*) gene (in red) and the centromeric probe for chromosome 7 (in green). Five/seven signals for each gene were detected per nucleus. *B,* In adenomatous hyperplasia specimen, the normal disomic pattern for *EGFR* gene was detected (two EGFR and centromeric signals/nucleus).

(Figures 3*A,B*). K-*ras* analysis showed TGT mutation only in BAC (codon 12 TGT). As the patient refused cytotoxic chemotherapy, she was started on Gefitinib treatment on December 2004, which was well tolerated, without diarrhea or significant cutaneous toxicity. On December 2005, chest CT showed a complete resolution of parenchymal infiltrates (Figure 1*B*). After 4 years of Gefitinib therapy at full dose, chest CT confirmed persistence of radiologic remission.

DISCUSSION

Complete remission of BAC have been reported after Gefitinib therapy.[1–3] To our knowledge, however, this represents the first case of prolonged remission of pathologically proven disseminated AAH associated with BAC. The long-term disease-free survival presented here shows that concurrent disomy of *EGFR* gene and absence of K-*ras* mutation can predict response to Gefitinib in AAH lesions, even in the absence of EGFR mutations.

Our experience suggests that long-term administration of Gefitinib might be effective in the management of AAH and multifocal BAC presenting as diffuse GGO, when fluorescence in situ hybridization or molecular testing are indicative of sensitivity.

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