

Case Report

A case of numerous atypical adenomatous hyperplasia diagnosed by a video-assisted thoracoscopic lung biopsy

Introduction

Atypical adenomatous hyperplasia (AAH) is a focal lesion often measuring 5 mm or less in diameter, in which atypical bronchioloalveolar cuboidal cells proliferate along the alveolar septa [1]. Although many cases of AAH, single or multiple, have been previously reported, no case with more than 100 AAH has ever been reported to the best of our knowledge. In this paper, we herein report a case of numerous AAH in a lung specimen obtained by video-assisted thoracoscopic lung biopsy. We also discuss the causal relationship between pathologically confirmed multiple AAH and mixed dust pneumoconiosis.

Case Report

A 46-year-old male was referred to our hospital due to abnormal opacities on chest X-rays lasting more than six months with no significant change in the number and size. The patient had never smoked, and he had a history of working as a plumber for about ten years. There was no family history of any malignant disease. He was diagnosed to have neurofibromatosis type I (NF-I) in his 30's. The peripheral blood tests showed no abnormalities. Chest X-rays showed small nodular opacities in both lower lung zones. Chest CT scans revealed multiple focal lesions with a hazy increased attenuation, measuring up to 10 mm in diameter, and present throughout both lungs, predominantly in the upper lobes. High-resolution CT (HRCT) scan disclosed multiple focal pure ground glass attenuation (GGA) (Figure 1). The number of lesions seen on the HRCT was, at least, more than 100. In the left apex, there was a small solid nodule measuring up to 6 mm in diameter surrounded with GGA (mixed GGA) (Figure 2). These lesions had no specific change in size and shape on follow-up CT examinations. In addition, no pleural thickening or pleural effusion was observed

To make a diagnosis, a video-assisted thoracoscopic wedge lung biopsy was performed, and left S¹⁺² was partially resected. During the operation, the pleural surface showed grayish-white multiple nodules. Microscopically, the mixed GGA lesion previously detected on HRCT consisted of anthracosis and interstitial fibrosis, and similar patchy fibrotic changes with anthracosis were present around the terminal airways (Figure 3a, 3b). In lung parenchyma, there were many lesions with relatively well-defined borders where slightly thickened alveolar septa were lined by cuboidal cells

(Figure 3c). Nuclear atypia was less marked. All these lesions were, therefore, diagnosed to be AAH. The size of each lesion was all less than 10 mm in the diameter and the number of AAH detected in microscopic field was 1.4 per cm². No mitotic figures or asbestos bodies were observed.

To date, sixteen months after the surgical lung biopsy, with no specific medical treatment, the patient's condition is well maintained with no significant changes in the remaining lung lesions on HRCT.

Discussion

AAH is defined as a localized proliferation of mild to moderate atypical cells lining the involved alveoli, and sometimes, the respiratory bronchioles, resulting in focal lesions in the peripheral alveolated lung, usually measuring less than 5 mm in diameter and generally in the absence of any underlying interstitial inflammation and fibrosis [1]. AAH is usually found as an incidental histological finding in resected lungs already bearing a primary lung cancer, especially adenocarcinoma [2]. In contrast, bronchioloalveolar carcinoma (BAC) is a special type of adenocarcinoma which shows the growth of neoplastic cells along the pre-existing alveolar structures without evidence of stromal, vascular, or pleural invasion [1]. Thus, AAH and BAC are morphologically similar and it is hypothesized that AAH is a putative precursor, or even an early-stage lesion, of a well-differentiated adenocarcinoma and BAC [3,4]. The evidence of epidemiological, morphological, morphometric, cytofluorometric, and genetic analyses also support this hypothesis [1]. The frequency of AAH ranges from 2-4% of non-cancer bearing patients to 23.2% in an autopsy series of patients with lung cancer [2,4]. Cases with multiple numbers of AAH have also been reported [2,3,5,6], but more than one hundred AAH in one patient has not been reported as far as we could determine.

The radiological findings of AAH are generally small non-solid nodules, or localized areas of complete or incomplete GGA with distinct borders and typically not visualized on chest radiographs [1]. However, resections of focal GGA reveal a range of pathology including AAH, BAC and invasive adenocarcinoma. Thus, it is often difficult to differentiate AAH from BAC only by radiological findings [7]. In our present case, we could identify countless AAH pathologically in surgically resected lung specimens, and we confirmed that those AAH to correspond with focal GGA on HRCT. However, we performed a pathological investigation of only a limited part of the whole lung, so whether all the GGA lesions are pathologically AAH or not remains unclear. Because focal GGA on HRCT appeared all alike, we believe that the lung was diffusely occupied by countless AAH.

Besides the findings of AAH, there were pathological manifestations of mixed dust pneumoconiosis predominantly present around the terminal airways. Mixed dust pneumoconiosis occurs when a mixture of silica and other less-fibrogenic dust is inhaled [8]. Its main histological feature is patchy

interstitial fibrosis that occurs predominantly in the area of respiratory bronchioles and adjacent small arteries with no silicotic nodules compared to silicosis [8]. Meanwhile, the AAH lesions located in the surrounding parenchyma, and intact alveolar area existed between the two pathological findings. Due to the patient's work experience as a plumber, he might have inhaled iron dust and stony dust during the labour, so the presence of mixed dust pneumoconiosis was understandable. Thomas *et al.* have reported a case of AAH, coexisting with primary lung adenocarcinoma and pleural mesothelioma in an asbestos-exposed subject [9], but the AAH resulting from inhaling industrial is not generally suggested. Therefore, mixed dust pneumoconiosis and AAH were likely to have little or no association with each other, and they most likely coexisted by chance.

NF-I, also referred to as von Recklinghausen's disease, is an autosomal dominant disease characterized by neurofibromas and abnormal cutaneous pigmentation (café-au-lait spot). The pulmonary manifestations of NF-I previously reported are GGA, bibasilar reticular opacities, bullae, cysts, and emphysema in the upper lobe [10]. Although there was a case of NF-1 with intense and widespread fibrosis and emphysematous change, which accompanied adenomatous hyperplasia in part, it was not diagnosed to be so-called AAH [11]. Therefore, the relationship between NF-1 and AAH still remains uncertain, as far as we could determine.

At present, the optimal clinical management of AAH lesions has not yet been determined. The efficacy of surgical resection for multiple pure GGA is reported [7]. However, it is also reported that the comparison of the postoperative survival in groups of lung cancer patients with, and without AAH showed no difference [12]. In most of the cases, an accurate distinction between AAH and adenocarcinoma is possible when it is based on pathological examinations, and diagnosing only by the preoperative radiological findings is very difficult. Therefore, a careful and precise follow-up of the primary lesion and also the remaining lung is considered to be necessary.

Conclusion

A rare case of numerous AAH pathologically diagnosed by a video-assisted thoracoscopic lung biopsy was described. To the present, 16 months after the lung biopsy, no apparent change in GGA on HRCT has been observed. The pathogenesis remains unknown despite the investigations. Nevertheless,

because AAH is recognized as a putative precursor of adenocarcinoma, we believe the further careful follow-up is optimal as a clinical management.

Key words: atypical adenomatous hyperplasia; ground glass attenuation; mixed dust pneumoconiosis

References

- [1] Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. World Health Organization Classification of Tumours. Pathology and Genetics Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press, 2004.
- [2] Nakahara R, Yokose T, Nagai K, Nishiwaki Y, Ochiai A. Atypical adenomatous hyperplasia of the lung: a clinicopathological study of 118 cases including cases with multiple atypical adenomatous hyperplasia. *Thorax* 2001;56(4):302-5.
- [3] Nomori H, Horio H, Naruke T, Suemasu K, Morinaga S, Noguchi M. A case of multiple atypical adenomatous hyperplasia of the lung detected by computed tomography. *Jpn J Clin Oncol* 2001;31(10):514-6.
- [4] Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. *Eur Respir J* 2001;18(6):1059-68.
- [5] Kishi K, Homma S, Kurosaki A, Tanaka S, Matsushita H, Nakata K. Multiple atypical adenomatous hyperplasia with synchronous multiple primary bronchioloalveolar carcinomas. *Intern Med* 2002;41(6):474-7.
- [6] Suzuki K, Takahashi K, Yoshida J, *et al.* Synchronous double primary lung carcinomas associated with multiple atypical adenomatous hyperplasia. *Lung Cancer* 1998;19(2):131-9.
- [7] Mun M, Kohno T. Efficacy of thoracoscopic resection for multifocal bronchioloalveolar carcinoma showing pure ground-glass opacities of 20 mm or less in diameter. *J Thorac Cardiovasc Surg* 2007;134(4):877-82.
- [8] Katzenstein AA. pneumoconiosis. In: *Surgical Pathology of Non-Neoplastic Lung Disease* 4th edition ed. Philadelphia, USA: Elsevier, 2006:132.
- [9] Thomas DH, Attanoos RL, Gibbs AR. Coexistent atypical adenomatous hyperplasia, primary lung adenocarcinoma and pleural mesothelioma in an asbestos-exposed subject. *Histopathology* 2004;45(5):540-2.
- [10] Chang ET, Hu WA, Lin CB, Lee JJ, Yang GG. Pulmonary manifestation in neurofibromatosis type 1. *Intern Med* 2007;46(8):527-8.
- [11] Yamamoto S, Hishinuma S, Tachibana K, *et al.* [Two cases of von Recklinghausen's disease with

diffuse pulmonary changes]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1996;34(2):226-30.

- [12] Suzuki K, Nagai K, Yoshida J, *et al.* The prognosis of resected lung carcinoma associated with atypical adenomatous hyperplasia: a comparison of the prognosis of well-differentiated adenocarcinoma associated with atypical adenomatous hyperplasia and intrapulmonary metastasis. *Cancer* 1997;79(8):1521-6.

Figure legends

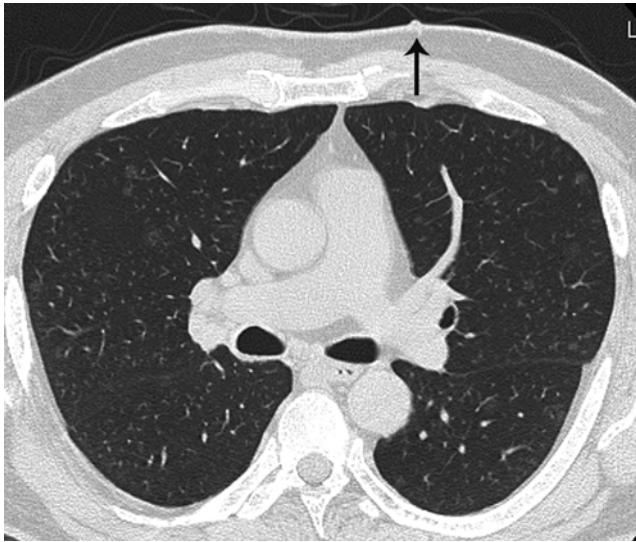


Figure 1. HRCT scan revealed multiple focal GGA throughout both lungs, measuring up to 10 mm in diameter. A polypoid lesion on the skin suggesting a neurofibroma was also seen (arrow).

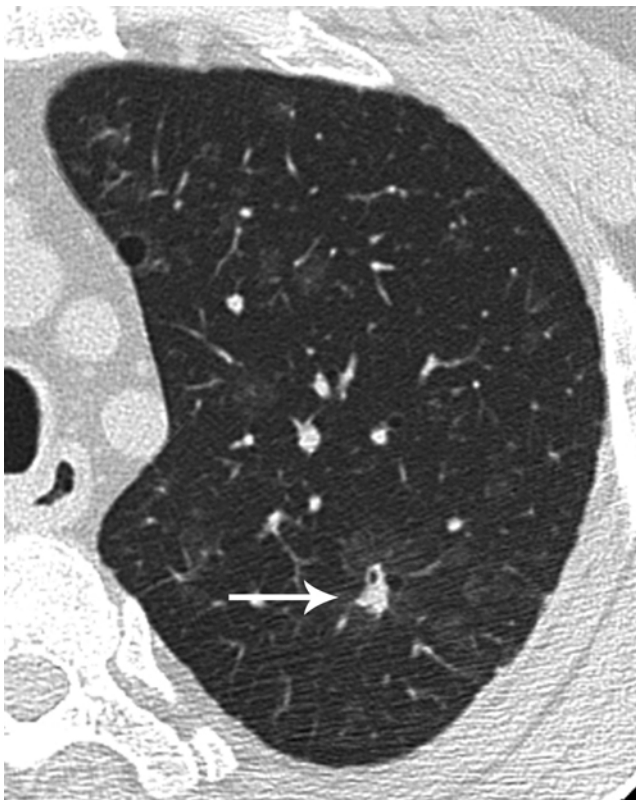


Figure 2. HRCT scan revealed multiple focal GGA, as well as a small solid nodule with 6 mm in diameter surrounded by GGA in the left apex (arrow).

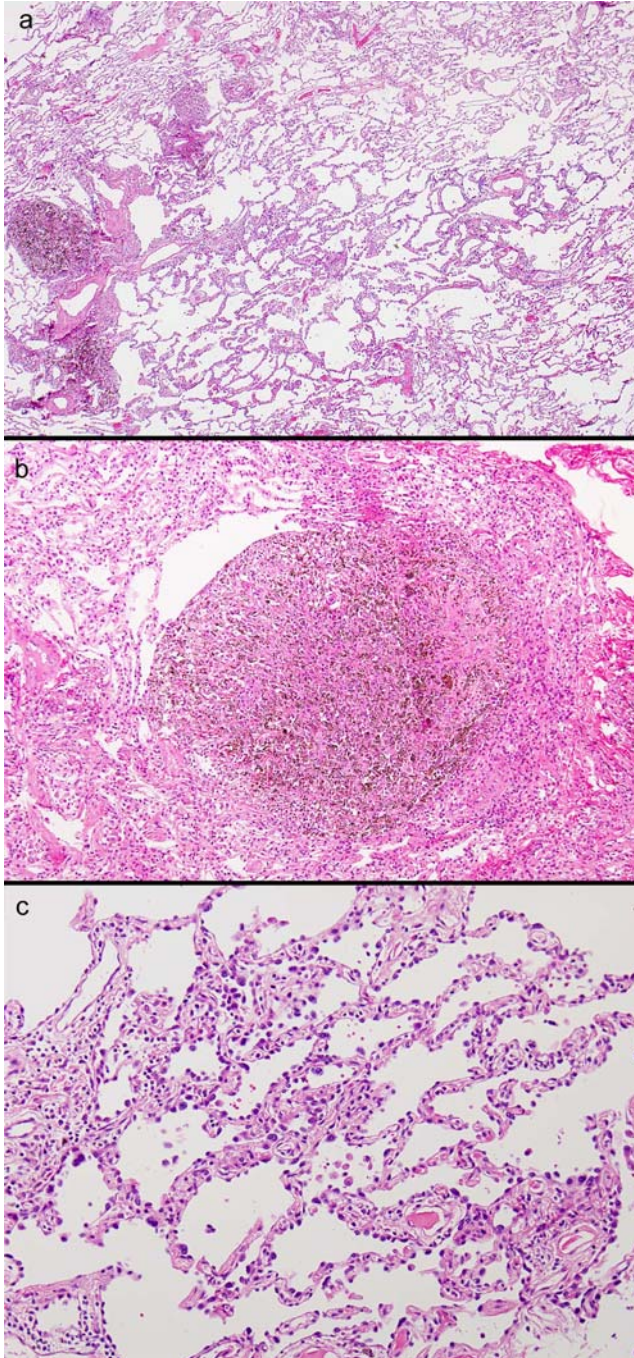


Figure 3. Microscopic findings of the specimen of the surgical lung biopsy. Anthracosis and fibrotic changes were present around the terminal respiratory tracts, and AAH were found in the alveolar area. AAH lesions had relatively well-defined boundaries, and a proliferation of atypical cuboidal cells was seen along the slightly thickened alveolar septa. (a): hematoxylin and eosin stain $\times 40$. (b)(c): hematoxylin and eosin stain $\times 100$.