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【 CASE REPORT 】

Allergic Bronchopulmonary Mycosis Complicated with Lung Adenocarcinoma

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Abstract:
Chest computed tomography (CT) of a 76-year-old woman with bronchial asthma showed multiple lung nodules with high CT densities that were compatible with high-attenuation mucoid (HAM) impactions characteristic of allergic bronchopulmonary mycosis (ABPM). Follow-up chest CT revealed increased sizes of multiple lung nodules. However, a left upper lobe nodule showed lower CT density than the other HAM impactions. A transbronchial lung biopsy of that upper lobe nodule revealed lung adenocarcinoma. Measuring the CT density is important for the differential diagnosis of lung nodules when following ABPM patients. Our patient's increased serum carcinoembryonic antigen levels were associated with peripheral blood eosinophilia. Mucoid impaction in the lung was positively stained with carcinoembryonic antigen and showed the distribution of eosinophilic granules.

Key words: allergic bronchopulmonary mycosis, asthma, carcinoembryonic antigen, eosinophil, high-attenuation mucus, lung cancer

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Introduction

Allergic bronchopulmonary mycosis (ABPM) results from type I and type III hypersensitivity reactions to fungi, especially *Aspergillus fumigatus*, and develops in patients with allergic conditions, such as bronchial asthma (1). Typical chest computed tomography (CT) findings of ABPM include central bronchiectasis, mucoid impaction, centrilobular nodules, consolidation, bronchial wall thickening, mosaic attenuation due to air trapping, pulmonary fibrosis, and enlarged mediastinal and hilar lymph nodes (2, 3). Mucoid impaction is caused by the increased accumulation of mucus and eosinophilic inflammation of the airways, which eventually leads to dilatation of the proximal bronchial walls, alternatively known as central bronchiectasis. The presence of high-attenuation mucoid (HAM) impactions on chest CT is diagnostic for ABPM (1, 4).

We herein report a patient with ABPM, for whom measurement of the CT densities of lung nodules was useful for the differential diagnosis of lung nodules and led to the discovery of lung cancer. Furthermore, increasing and sequentially fluctuating levels of serum carcinoembryonic antigen were associated with fluctuating levels of peripheral blood eosinophilia.

Case Report

A 76-year-old woman had been treated for bronchial asthma since 60 years old by the combination of the inhaled corticosteroid fluticasone furoate plus the long-acting beta 2 agonist vilanterol, the leukotriene receptor antagonist montelukast, and the mucolytic fudosteine. She had never smoked and had no history of other allergic diseases, including allergic rhinosinusitis. Her asthma had been well controlled by these medications; however, blood testing revealed peripheral blood eosinophilia (1,290/μL), an increased level of total serum immunoglobulin E (IgE) (maximum 327.9 IU/mL), and positive results of IgE specific for various fungi, including *Aspergillus*, *Candida*, *Cladosporium*, and

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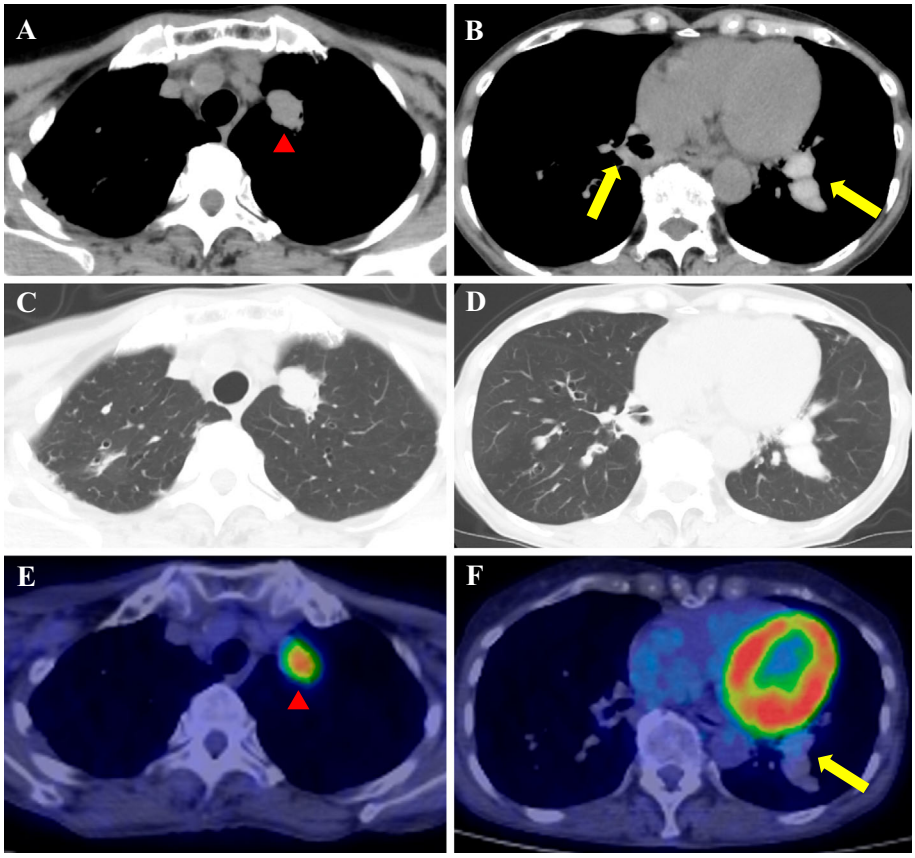

Figure 1. **Chest computed tomography (CT) scans (A-D) demonstrating multiple lung nodules with different CT densities. A left upper lung nodule (A, red arrowhead) showed a low CT density [35-50 Hounsfield units (HU)], but the right and left lower lung nodules (B, yellow arrows) had high CT densities of 98-114 HU, which were compatible with high-attenuation mucoid (HAM) impactions. Chest 18F-fluorodeoxyglucose (FDG)-positron emission tomography revealed an increased FDG uptake in the left upper lung nodule (E, red arrowhead), showing a standardized maximum uptake value (SUV_{max}) of 5.9, which was higher than the SUV_{max} of 1.4 of the HAM impaction in the left lower lobe (F, yellow arrow), suggesting that the nodules had different properties.**

Penicillium species. The *Aspergillus* antibody measured by the complement fixation test was negative.

Chest CT showed multiple lung nodules with high CT densities in the bilateral lower lobes that were consistent with HAM impactions with central bronchiectasis. A cytological examination of bronchial washing fluid obtained during bronchoscopy identified *Aspergillus* hyphae and Charcot-Leiden crystals. Based on the new Japanese diagnostic criteria, these findings were diagnosed as indicative of ABPM (1).

The patient's serum carcinoembryonic antigen (CEA) levels were increased, fluctuating between 10-20 ng/mL (normal range <5.0 ng/mL) in accordance with the appearance of HAM impactions. Follow-up chest CT performed seven years later revealed that multiple lung nodules had increased in size. A lung nodule in the apex of the left upper lobe showed a lower CT density [35-50 Hounsfield units (HU)] than many other HAM impactions, which showed relatively high CT densities (98-114 HU (Fig. 1). Since the CT density of the lung nodule in the left upper lobe was different from the densities of the HAM impactions, and the patient's CEA level had increased to 29.0 ng/mL, we suspected that the left upper lung nodule was a malignant lung tumor.

A transbronchial lung biopsy specimen and cytological examination of the left upper lung nodule provided evidence of lung adenocarcinoma (Fig. 2). Contrast-enhanced brain magnetic resonance imaging and 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT were negative for evidence of systemic metastatic disease. The FDG uptake by the left upper lung nodule (Fig. 1E), with a standardized maximum uptake value (SUV_{max}) of 5.9, was higher than the HAM impaction in the left lower lobe, with an SUV_{max} of 1.4 (Fig. 1F).

The patient underwent left upper lobectomy and resection of the N2 mediastinal lymph nodes. The final diagnosis of the left upper lung nodule was stage IIIA (pT2aN2M0) papillary adenocarcinoma with an exon 19 deletion of the epidermal growth factor receptor gene. Immunohistochemistry of lung adenocarcinoma in the left upper lobe obtained by surgical resection revealed that the tumor was positive for CEA staining (Fig. 2C). The patient then received four cycles of chemotherapy consisting of carboplatin plus pe-

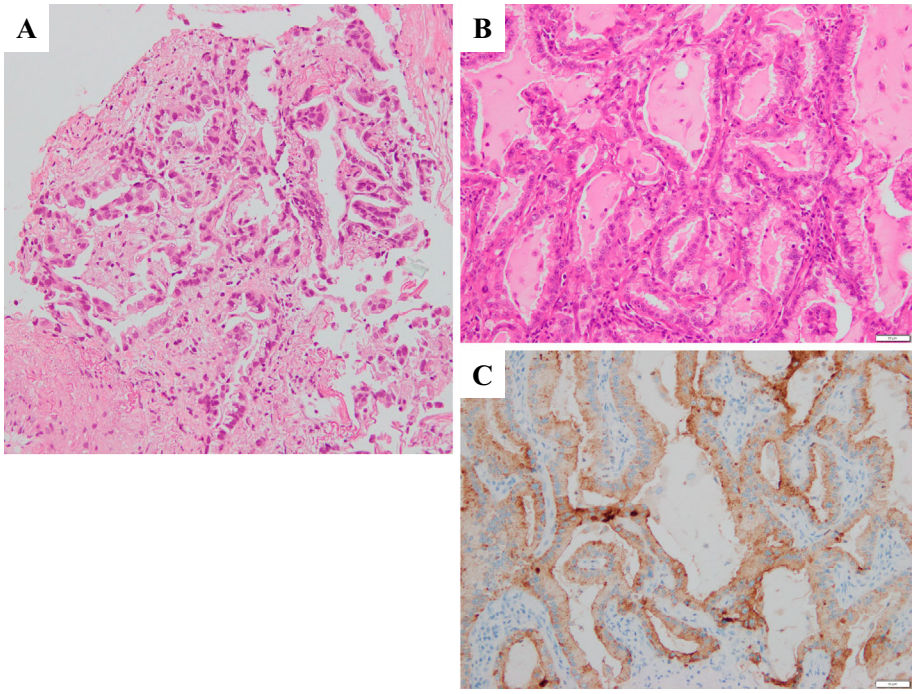

Figure 2. **A transbronchial lung biopsy specimen from the left upper lung nodule revealed adenocarcinoma [Hematoxylin and Eosin (H&E) staining, A]. H&E staining (B) and immunohistochemical staining of carcinoembryonic antigen (CEA) (C) of the surgically resected left upper lung lobe revealed that adenocarcinoma was positively stained with CEA. Original magnification ×200.**

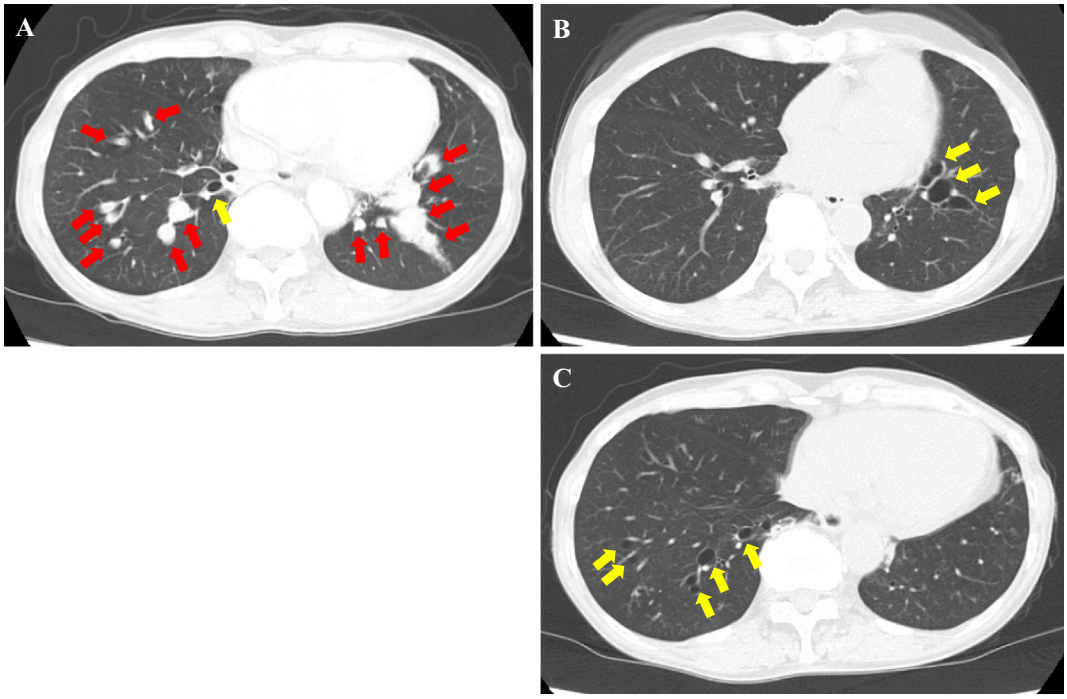

Figure 3. **Chest computed tomography (CT) before (A) and after (B, C) treatment of lung cancer showing the disappearance of high-attenuation mucoid (HAM) impactions (red arrows) and the presence of central bronchiectasis (yellow arrows).**

metrexed. The patient has been free from recurrence of the lung cancer, and the HAM impactions have been gone for more than 4.5 years, with her serum levels of CEA decreasing to <13.8 ng/mL (Fig. 3, 4).

Discussion

This case demonstrates the importance of measuring the CT density to differentiate lung cancer from HAM impac-

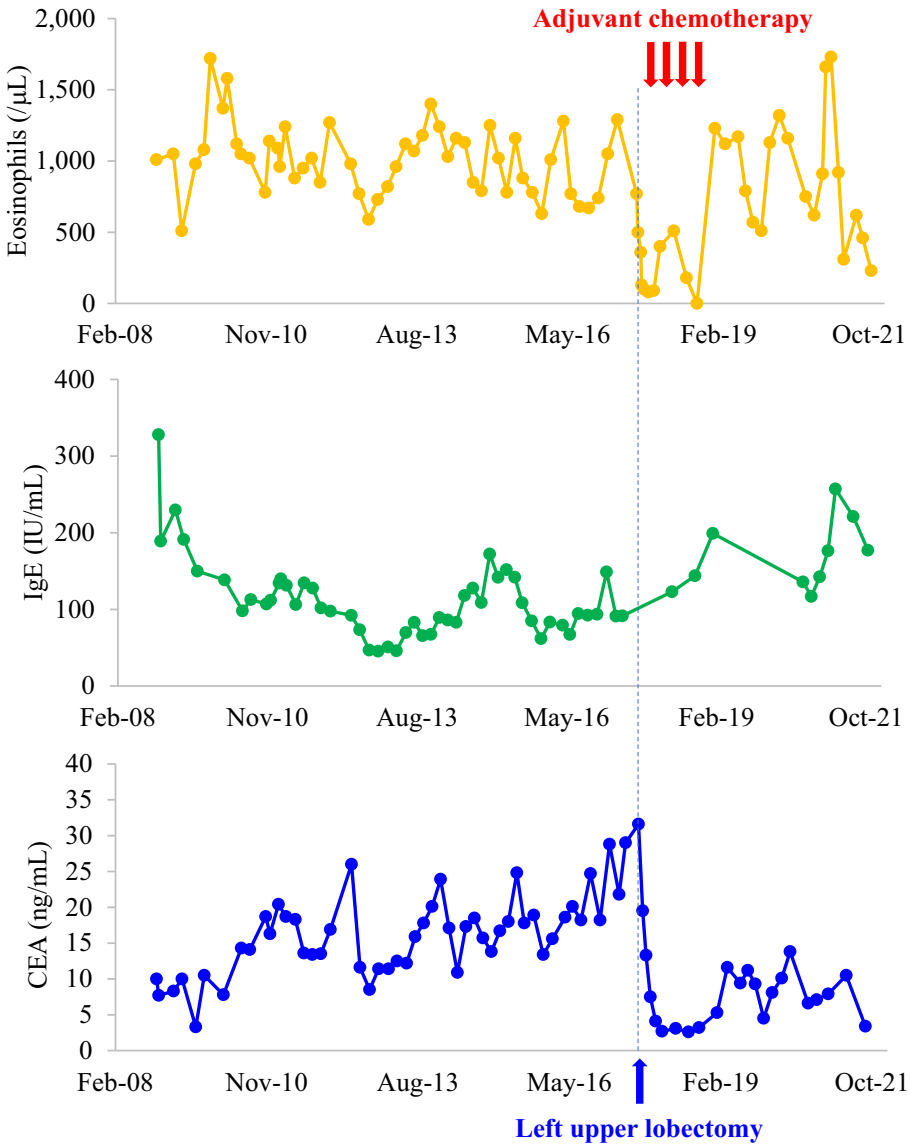

Figure 4. Sequential changes in serum carcinoembryonic antigen (CEA) levels before and after surgical resection of the lung adenocarcinoma in the left upper lobe. Serum CEA levels were dramatically decreased after resection of the lung tumor and 4 subsequent cycles of adjuvant chemotherapy, for which dexamethasone (6.6 mg) was administered on Day 1 for premedication, in accordance with disappearance of the high-attenuation mucoid (HAM) impactions.

tions in a patient with ABPM. Mucoid impactions are divided into HAM and non-HAM impactions on chest CT. HAM is a chest CT finding that is characteristic of ABPM. It has been reported in 18.7% to 30% of patients with ABPM (4). The sensitivity and specificity of HAM impactions for ABPM were reported to be 39.7% and 100%, respectively (5). The proposed cut-off value of the CT density for a HAM impaction is 70 HU (6). A CT density greater than 100 HU is significantly correlated with increased levels of serum IgE and peripheral blood eosinophils (6). The bronchial asthma, central bronchiectasis with mucoid impaction, HAM impactions concomitant with marked peripheral blood eosinophilia (1,290/μL), IgE positivity specific for various fungi, and presence of *Aspergillus* hyphae in bronchial washing fluid of the present patient were diagnostic for ABPM according to the new Japanese diagnostic criteria (1). However, one of the lung nodules showed a different CT density, which suggested concomitant lung cancer. Thus, measurements of CT density were useful for our patient because they enabled us to identify her lung malignancy.

Another interesting and important finding in this patient was that her serum CEA levels fluctuated (Fig. 4) in accordance with the appearance and disappearance of her HAM impactions. CEA is produced by the epithelium of not only the intestinal tract but also the respiratory tract. It plays an important role in cell adhesion (7). Serum CEA levels are increased in patients with lung, gastric, colorectal, pancreatic, and breast cancers. Increased serum levels of CEA in patients with hypereosinophilia and/or various eosinophilic lung diseases have been reported (8-11). Serum CEA levels were elevated in a patient with eosinophilic bronchiolitis and sinusitis with overexpression of CEA in the lung and sinus.

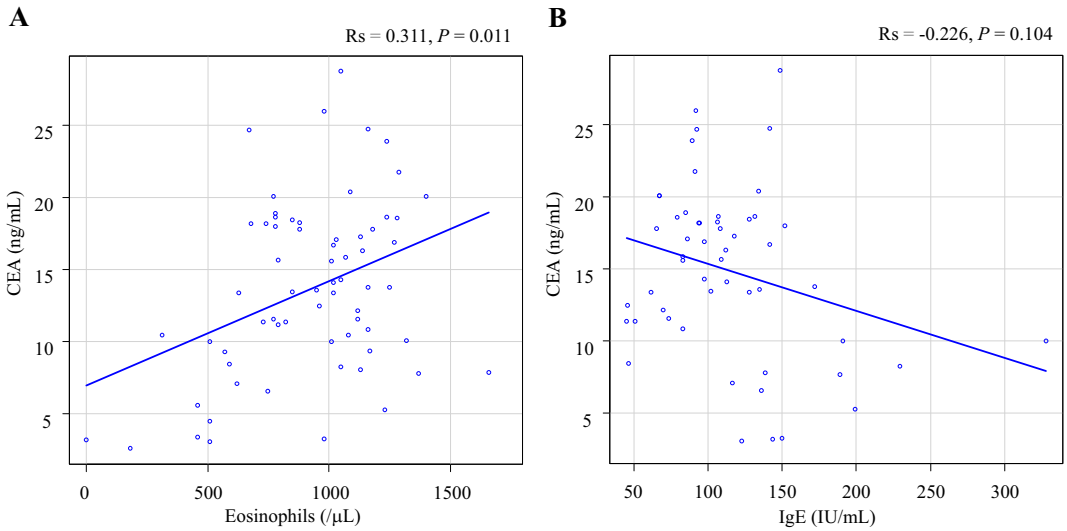

Figure 5. **Correlations between levels of serum CEA and serum IgE and the eosinophil counts during the clinical course of the patient (A: serum levels of CEA vs. eosinophil counts, B: serum levels of CEA vs serum IgE).**

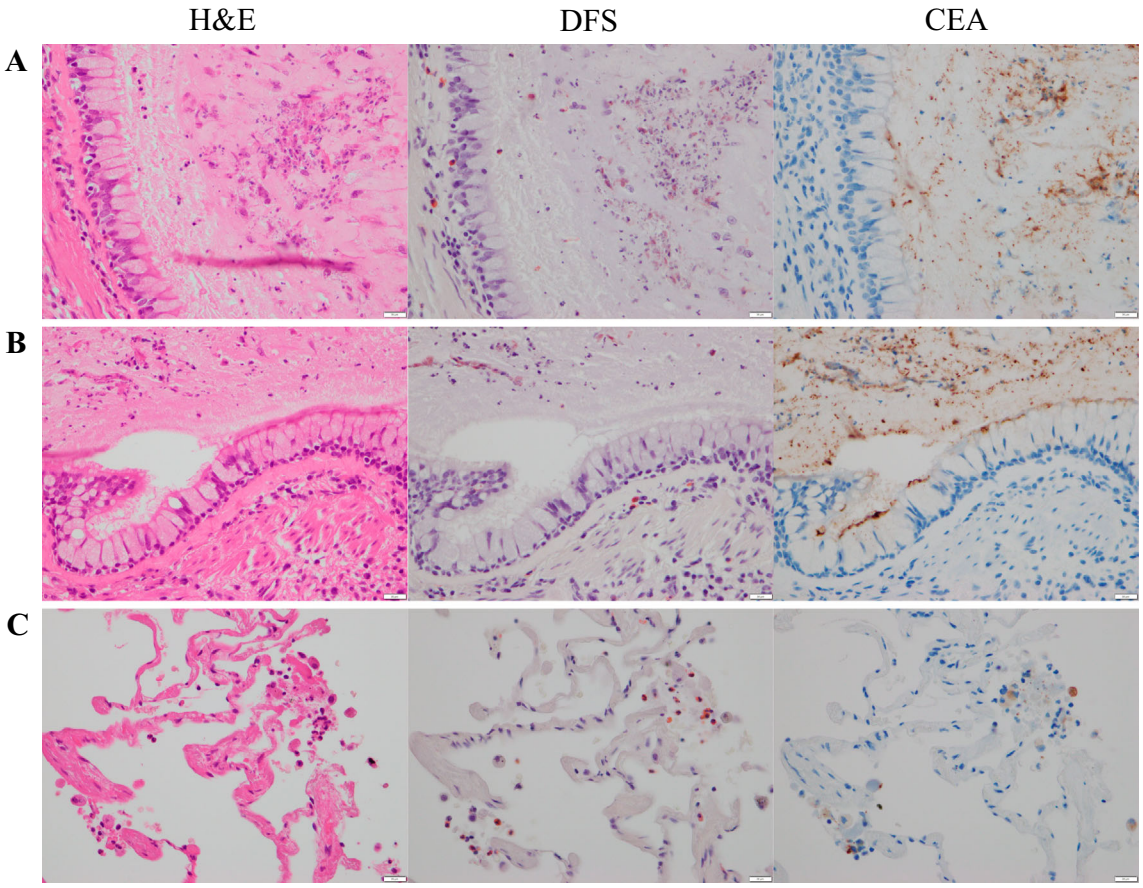

Figure 6. **Lung specimen from the surgically resected left upper lung lobe for which Hematoxylin and Eosin staining, direct fast scarlet 4BS (DFS), and immunohistochemical staining of carcinoembryonic antigen (CEA) revealed mucoid impaction (substances on the right side of A and on the upper side of B) that was positively stained with CEA, along with the distribution of eosinophil extracellular trap cell death (ETosis)-derived acidophilic granules (stained orange by DFS staining). The luminal side of the bronchial epithelial goblet cells was also stained with CEA (B), suggesting that the cell polarity had been maintained compared to the adenocarcinoma shown in Fig. 2C. Alveolar macrophages and some eosinophils in the alveolar space were weakly stained with CEA (C). The eosinophils were stained orange by DFS staining. Original magnification ×400.**

Both the serum levels and overexpression of CEA were improved in that patient by treatment with systemic corticosteroids (10).

Serum CEA levels were elevated in some patients with ABPM and decreased after resolution of consolidation shadows as a result of corticosteroid treatment (12). A recent study found that the expression of CEA by eosinophils in tissues of the respiratory tract affected by ABPM was greater than the expression in normal lung tissues. It also found that serum CEA levels were positively correlated with eosinophil counts, suggesting that activated eosinophils affect the levels of CEA secretion (13). We plotted the sequential data for the serum CEA and IgE levels and the peripheral blood eosinophil counts measured over our patient's clinical course, other than the data during adjuvant chemotherapy and five months after concluding chemotherapy in order to exclude the effects of systemic corticosteroids, and found a significant correlation between her serum CEA levels and eosinophil counts (Spearman's rank correlation coefficient Rs=0.311, p=0.011, Fig. 5; The data were analyzed by EZR version 1.55.) (14) but not between her serum CEA and IgE levels (Rs=-0.226, p=0.104) or between her eosinophil counts and IgE levels (Rs=0.00915, p=0.946). Furthermore, we examined the immunohistochemistry of CEA and found that mucoid impaction in the lung was positively stained with CEA, with the distribution of eosinophil extracellular trap cell death (ETosis)-derived acidophilic granules also noted (Fig. 6). These findings, along with the positive staining of CEA in the adenocarcinoma, suggest that the increased levels of serum CEA may have been derived not only from lung adenocarcinoma but also from mucoid impaction associated with eosinophilic inflammation.

In our patient with ABPM, elevated serum CEA levels appeared to be associated with eosinophilic inflammatory activity. However, the detailed mechanism underlying the elevated CEA levels remains unclear. A recent study found that the tumor cell expression of the alarmin cytokine interleukin-33, which is also important for the activation of group 2 innate lymphoid cells in allergic diseases, was necessary and sufficient for eosinophil-mediated antitumor responses in a mouse model (15). Eosinophils are increased in various types of cancer in association with the granulocyte-macrophage colony-stimulating-factor-dependent pathway and are associated with the overall survival (16). Taken together, these findings suggest that eosinophils, CEA, and cancer are closely associated with each other.

Conclusions

Measurement of the CT densities of lung nodules is important during follow-up of patients with ABPM. If the size of a lung nodule is increased and/or its CT density is different from other HAM impactions, the possibility of other another disease, such as lung cancer, should be considered. Elevated serum CEA levels appeared to be associated with eosinophilic inflammatory activity in our patient with ABPM.

The authors state that they have no Conflict of Interest (COI).

References

1. Asano K, Hebisawa A, Ishiguro T, et al. New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation. J Allergy Clin Immunol **147**: 1261-1268.e5, 2021.
2. Agarwal R, Sehgal IS, Dhooria S, Aggarwal A. Radiologic criteria for the diagnosis of high-attenuation mucus in allergic bronchopulmonary aspergillosis. Chest **149**: 1109-1110, 2016.
3. Kaur M, Sudan DS. Allergic bronchopulmonary aspergillosis (ABPA) - the high resolution computed tomography (HRCT) chest imaging scenario. J Clin Diagn Res **8**: RC05-RC07, 2014.
4. Agarwal R, Gupta D, Aggarwal AN, Saxena AK, Chakrabarti A, Jindal SK. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. Chest **132**: 1183-1190, 2007.
5. Agarwal R, Khan A, Gupta D, Aggarwal AN, Saxena AK, Chakrabarti A. An alternate method of classifying allergic bronchopulmonary aspergillosis based on high-attenuation mucus. PLoS One **5**: e15346, 2010.
6. Phuyal S, Garg MK, Agarwal R, et al. High-attenuation mucus impaction in patients with allergic bronchopulmonary aspergillosis: objective criteria on high-resolution computed tomography and correlation with serologic parameters. Curr Probl Diagn Radiol **45**: 168-173, 2016.
7. Maxwell P. Carcinoembryonic antigen: cell adhesion molecule and useful diagnostic marker. Br J Biomed Sci **56**: 209-214, 1999.
8. Iwata H, Tsuboi N, Ishii T, et al. Hypereosinophilia associated with increased serum levels of carcinoembryonic antigen. Intern Med **47**: 963-967, 2008.
9. Ashitani J, Sakamoto A, Maki H, et al. A case of eosinophilic pneumonia with elevated levels of carcino-embryonic antigen (CEA). Nihon Kyobu Shikkan Gakkai Zasshi **32**: 1194-1198, 1994 (in Japanese).
10. Yanagitani N, Shimizu Y, Kazama T, Dobashi K, Ishizuka T, Mori M. Eosinophilic bronchiolitis indicating eosinophilic airway disease with overexpression of carcinoembryonic antigen in sinus and bronchiole: case report. J Biol Regul Homeost Agents **24**: 99-102, 2010.
11. Tang TT, Cheng HH, Zhang H, et al. Hypereosinophilic obliterative bronchiolitis with an elevated level of serum CEA: a case report and a review of the literature. Eur Rev Med Pharmacol Sci **19**: 2634-2640, 2015.
12. Noguchi T, Yamamoto K, Moriyama G, et al. Evaluation of serum levels of carcinoembryonic antigen in allergic bronchopulmonary aspergillosis. J Nippon Med Sch **80**: 404-409, 2013.
13. Yang Y, Gao Q, Jin Y, Qi M, Lu G, HequanLi. Eosinophils may serve as CEA-secreting cells for allergic bronchopulmonary aspergillosis (ABPA) patients. Sci Rep **11**: 4025, 2021.
14. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant **48**: 452-458, 2013.
15. Hollande C, Boussier J, Ziai J, et al. Inhibition of the dipeptidyl peptidase DPP4 (CD26) reveals IL-33-dependent eosinophil-mediated control of tumor growth. Nat Immunol **20**: 257-264, 2019.
16. Wechsler ME, Munitz A, Ackerman SJ, et al. Eosinophils in health and disease: a state-of-the-art review. Mayo Clin Proc **96**: 2694-2707, 2021.