

Case Report

Mucormycosis lung cavity accompany with serum IgG4 elevation: a case report

Li-Hua Wang¹, Fen Lan², Yan-Bin Tan¹, Jin-Long Tang³

Departments of ¹Radiology, ²Respiratory, ³Pathology, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Received December 10, 2017; Accepted September 5, 2018; Epub October 15, 2018; Published October 30, 2018

Abstract: Background: Mucormycosis is not common in patients of normal immune condition. Multiple large lung thick-wall cavities with blood-stained sputum suggest special inflammation. Isolated pulmonary mucormycosis is extremely rarely reported, along with elevated serum IgG4 and pathological discovery of IgG4⁺ cell may be misdiagnosed as IgG4-related disease and cause therapy dilemma, especially when the microbiology and pathologic results are uncertain because of scattered regressive fungal hyphae, negative acid-fast staining and sputum culture. Since IgG4 elevation can be seen in a variety of inflammatory conditions, the characteristics of IgG4 as poor crosslinking with antigens and the specificity of antibodies, neither complement deposition associated to IgG4, mucormycosis along with elevated serum IgG4 should be among differential diagnosis of fungus and imaging could provide more information. Case presentation: A 31-year-old man employed as a paper cutting worker for 7 years complained irritate cough without product for 2 months with weight loss, 1 month ago he had progressive nausea and sour regurgitation, with occasional blood-stained sputum, no fever and chest pain. CT revealed multiple mass in bilateral lung and obstruction of the right upper lobe bronchus. Serum IgG4 elevated. Bronchoscope and TBNA found no malignancy proof. There was no evidence of diabetes mellitus and connective tissue diseases. Enhanced MRI revealed masses contained cavity 18 days after CT. CT guided needle aspiration biopsy was performed and pathological diagnosis confirmed necrotic granuloma with IgG4⁺ cell and regressive fungus. Considered the possible diagnosis of IgG4 related lung disease, the patient underwent 6 days' methylprednisolone intravenous drip (60 mg/d). Follow-up CT demonstrated unexpected progressed. The patient dismissed to another hospital and his pathological slides were rechecked and mucormycosis was suspected. Accord with image diagnosis he underwent tentatively therapy with liposomal amphotericin B and improved three months later. Conclusions: Mucormycosis manifested as multiple large lung thick-wall cavity with elevated serum IgG4 may be missed as IgG4-related disease and cause therapy dilemma, especially when the pathologic result is not certain. Image feature could be determinative and help differentiated.

Keywords: Mucormycosis, cavity, IgG4-related disease, radiology

Introduction

Pulmonary mucormycosis is uncommon in lungs (24%) and in the form of disseminated disease (6%) [1]. The mortality associated with pulmonary mucormycosis is as high as over 60%, with inappropriate treatment. With the exception of rhino-cerebral and cutaneous mucormycosis, the clinical diagnosis of mucormycosis is difficult. Patients who had no obvious abnormal immunity has a chance of infected occasionally [2]. Diagnosis by imaging along is difficult, because lesions may be non-specific and cannot be differentiated from those

of invasive aspergillosis [1], follow up study may provide clue of correct diagnosis. Although IgG4 elevation can be seen in a variety of inflammatory conditions, it had not been reported in mucormycosis. Here we report a case of mucormycosis present as multiple large lung thick-wall cavities with elevated serum IgG4 missed as IgG4-related disease.

Case report

A 31-year-old man complained irritate cough without product for 2 months with weight loss. He had progressive nausea and sour regurgita-

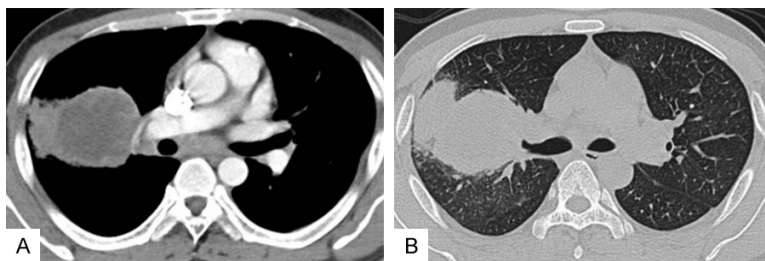


Figure 1. Enhanced CT. Mediastinal window (A) shows large cavity located in right upper lobe adhesion with a patchy opacity in distal lung. Subcarinal lymph nodes enlarged. Lung window (B) shows blur exudation in peripheral region.

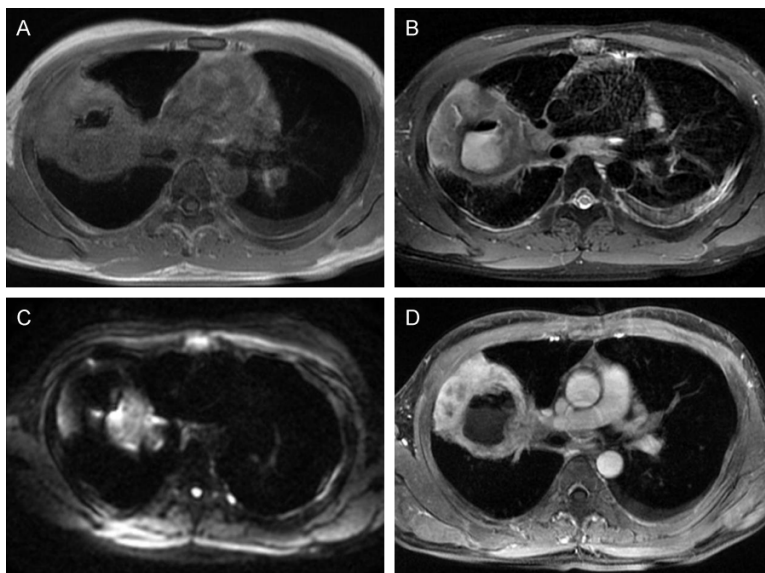


Figure 2. Enhanced pulmonary MR: Axial T1WI (A) and T2WI (B) showed iso-hyper signal intensity of the wall and fluid-fluid level within high signal intensity. DWI images showed high in proximal wall and low signal intensity inside (C). Dynamic enhanced MRI (D) showed the thick wall enhanced gradually and heterogeneously, especially the peripheral region. Several groups of hilar and mediastinal lymph nodes enhanced.

tion 1 month ago and blood-stained sputum occasionally. He had been working as a paper cutter in a printing plant for 7 years. One week before, his discomfort aggravated with night sweat, no fever or chest pain. CT of local hospital revealed multiple masses in bilateral lung and neoplasm was suspected. He was admitted by respiratory department of our hospital. Physical examination found a white ulcer in the left wall of oral cavity. Relevant test of blood results were as followed. WBC: $9.5 \times 10^9/L$; NEU%: 64.2%; ESR: 88.00 mm/H; Serum IgG: 24.16 g/L; IgG4: 25.30 g/L; PPD: (-); T-SPOT: (-), Blood G test: $< 10.00 \text{ pg/ml}$ and GM test: (-), Total IgE: $> 2000.01 \text{ U/ml}$. Sputum smear nega-

tive. Anticardiolipin antibody and Anti-neutrophilcytoplasmic antibodies (ANCA) and antinuclear antibodies were all negative. Considered that there might exist unknown pathogens, the patient underwent Meropenem 1 g intravenous q8h for one week and symptoms of cough hemoptysis improved.

Enhanced HRCT was performed 3 d after admitted and revealed bilateral rounded or elliptical masses contained necrosis measured 10 cm-14 cm. All had clear margin and inside showed heterogeneous lower density than outside. The largest lesion of right upper lobe adhered with a patchy opacity in distal lung and connected with lesion in the middle lobe. The initiation part of bronchial in anterior segment of right upper lobe was obstructed. In plain scan the peripheral region of mass measured 37 Hu, and raised up to 57 Hu after enhancement in artery phase (38 s after contrast medium injection) and 61 Hu in delay phase (60 s after contrast medium injection). Enlarged lymph node was defined as short axis diameter beyond 10 mm. Mediastinal lymphaden-

ectasis displayed in 4R, 7, 5 groups and right hilar zones and showed slightly enhanced (**Figure 1**).

To find out the reason of obstruction of the right upper lobe bronchus, bronchoscope was performed in the 4th day after admitted and confirmed the obstruction. Pathologic results displayed bronchial mucosa chronic inflammation with erosion. Ultrasound explored 4R and 7 group lymph nodes hypoechoic homogenous clear margin mass. Lymph nodes puncture with TBNA was performed and pathologic smear showed lymphocyte and bronchial mucosa. No malignant lesion was found.

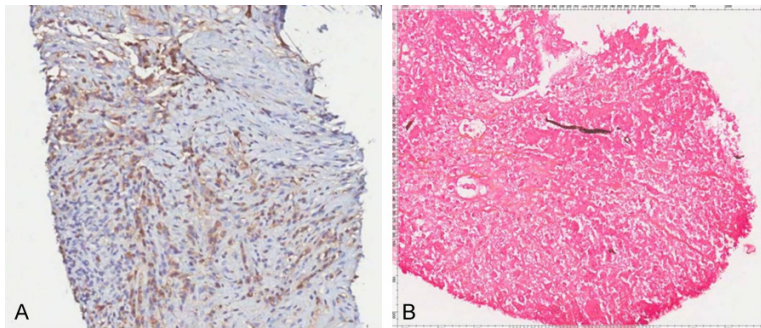


Figure 3. A. Specimen from CT-guided needle puncture in hematoxylin and eosin-stained sections revealed fibrous tissue degeneration accompanied with small amount of inflammatory cell. Note the regressive fungal hyphae. B. Immunostaining of IgG4 reveals IgG4⁺ plasma cells (Magnification in $\times 200$).

After bronchoscope CA125 was found elevated to 92.3 U/mL, in order to determine the characteristic of the lesion, enhanced pulmonary MRI was performed 16 d days later. MRI showed cavities with fluid-fluid level. The cavity wall showed iso-signal intensity in T₁WI (**Figure 2A**) and iso-to hyper-signal intensity in T₂WI (**Figure 2B**), inside was low signal intensity in T₁WI and high in T₂WI indicate liquefaction necrosis. DWI images showed high in proximal wall and low signal intensity inside (**Figure 2C**). Dynamic enhanced images showed the thick wall enhanced gradually and heterogeneously. Hilar and mediastinal lymph nodes also enhanced (**Figure 2D**). There was newly appeared small amount of pleural effusion in the left cavity.

Since thick wall cavity could be caused by mucormycosis or invasive aspergillosis, paranasal sinus CT was performed and showed no abnormality. In order to confirm the diagnosis, CT guided needle aspiration biopsy was performed at right upper lobe lesion. Pathologic findings showed hyperplasia fibrosis and inflammatory granulation tissue with coagulative necrosis in the right lung specimen. Special staining of PAS and PASM staining showed scattered regressive fungal hyphae, acid-fast staining was negative. Reticular fiber staining was positive. Immunohistochemistry staining showed necrotic granuloma with IgG4⁺ and IgG⁺ cell (**Figure 3**).

Considered the possible diagnosis of IgG4-RD the patient was admitted by rheumatism and immunity department 9 days after admitted and underwent 6 days' methylprednisolone intravenous drip (60 mg/d) along with support-

ive treatment. However, follow up CT showed cavities enlarged and the patient transferred next day to Peking Union Medical College Hospital, exacerbated with dyspnea and hemoptysis as soon as he was admitted and lasted for 2-3 d. Based on the same set of pathologic pictures, one reported IgG4⁺ cell count about 30/HPF and IgG4⁺/IgG⁺ > 40%, IgG4-RD still can't be ruled out. But other pathologic doctors considered that the irregular fungal hyphae been muco while the genus and specie of fungus was hard to recognized. Since image findings might accord with muco they treated the patient with liposomal amphotericin B intravenous 60 mg/QD for one month, dyspnea and hemoptysis stopped. Lung cavities turned into thin-walled and serum IgG4 decreased. Till then the diagnosis is finally confirmed to be pulmonary mucormycosis but not IgG4-RD. Three months follow-up back in our hospital showed serum IgG4 declined to 6.61 g/L.

Discussion

In this case, the clinical manifestation is non-specific. The patient has been worked as paper-cutting worker for 7 years, which may indicate an environment with inhaled particles and high risk for fungal infection. Pulmonary mucormycosis is an uncommon but life-threatening opportunistic infection usually accompanied with immune-compromised individuals [8, 9]. Fungal culture of the specimens was found to be positive only in half of the patients. Treatment with liposomal amphotericin B was associated with a 67% survival rate [10].

Pulmonary mucormycosis may present on chest imaging with focal consolidation, lung masses, pleural effusions, cavities, or multiple nodules [11]. In this case HRCT manifested was more informative and determinative to the patient, as masses followed by thick-walled cavity, no halo sign, nor subsequent changes appeared in typical mucormycosis include infiltrates, consolidation, cavitation, focal masses, or nodules. Mucormycosis alone has sequen-

tial morphological and pathologic changes. In CT it showed halo sign initially and then reversed-halo sign represents internal infarction with peripheral consolidation. Consolidation or masses may develop cavity with air-fluid level [12]. Mucormycosis abscess may have air-fluid level and should be differentiated with pyogenic bacteria. It could mimic other granuloma [13].

Differential diagnoses included the necrotizing granulomatous lesions caused by other fungus such as *Aspergillus*, in which large thick-walled cavity is not often seen, necrosis maybe not so thoroughly and cause slit-like or sticky fluid inside [14, 15]. ANCA-related vasculitis may develop thick-walled cavities but basically appear multiple and accompanied with nodules and exudation [16]. Tuberculosis may present cavity with satellite lesion such as calcification, fibrosis, hyperplasia lesion and adjacent pleural thicken. Inflammatory pseudotumor may manifest irregular patchy opacity rather than thick-walled cavities with fluid level.

Although IgE concentration > 2000 IU/ml, ABPA can rule out by negative blood G and GM test along with image feature. The patient's serum CA125 elevated to 92.3 U/mL may due to pleural effusion.

In this case, (≥ 1.35 g/l); IgG4⁺ cell > 10 cells/HPF; IgG4⁺/IgG⁺ > 40%, met the IgG4-RD comprehensive diagnostic criteria in 2011 [3-5]. There no similar report about IgG4 elevated in pulmonary mucormycosis. Since the diagnosis of IgG4-RD was denied by the fact that hormone therapy deteriorated the cavity lesions, elevated serum IgG4 level did caused diploma of therapy.

IgG4-related disease had been described in 1961, but the knowledge about this phenomenon is very poor. It is believed that a type 2 T-helper (Th2) cell mediated immune response, followed by activation of regulatory T cells (Treg), lead to increased expression of interleukins, mainly IL-4, 5, 10, 13 and TGF-beta. These cytokines contribute to the increase in IgG4 production. It is not clear whether immune complexes (mainly by IgG4) are mediating tissue damage or this phenomenon is secondary. It could be induced that opportunistic infection aroused up-regulated responses of Th2 and Treg, therefore stimulated production of IgG4 and infiltration of IgG4⁺ plasma cells in affected

tissues through IL-21 [3]. Th2 induces an allergic immune response with eosinophilia and increased serum IgE, which can be demonstrated by total IgE > 2000.0 IU/ml in this patient.

IgG4-related lung disease could be categorized into four major image subtypes: solid nodular type having a solitary nodular lesion that included a mass; multiple round shaped ground-glass opacity (GGO); alveolar interstitial type and bronchovascular type [6, 7]. Lung mass and cavity is uncommon manifestation of IgG4-RD according to Dai [7]. IgG4-RD in lung rarely had thick wall cavity [17-20]. Solid nodular reported by Dai is 6.5 cm and accompany with GGO and thickening of bronchovascular bundles and interlobular septa. Intrathoracic lymphadenopathy is more common and can be detected in half or more of patients with IgG4-RD [21]. Differential diagnosis also includes primary lung cancer and metastasis. Intrathoracic lymphadenopathy has no value in differential diagnosis [22].

Conclusion

The IgG4 finding does not in itself demonstrate IgG4 disease. IgG4 elevation can be seen in mucormycosis with unknown reason. In opportunistic infection as pulmonary mucormycosis imaging feature was determinative and resolve therapy dilemma or guiding biopsy.

Acknowledgements

We thanks Dr. Rong Zhang provide instruction about microbiology. The author thanks the national sci-tech support plan foundation of China under contract 2016YFC1300304 for their great support.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Li-Hua Wang, Department of Radiology, The Second Affiliated Hospital of Zhejiang University School of Medicine, 88 Jiefang Rd, Hangzhou 310009, Zhejiang, China. Tel: +86-571-8820-8439; Fax: +86-571-8820-8439; E-mail: lihuawang@zju.edu.cn

References

- [1] Binder U, Maurer E, Lass-Flörl C. Mucormycosis: an emerging disease? Clin Microbiol Infect 2006; 12: 7-23.

Mucormycosis missed as IgG4-related disease

- [2] Prabhu RM, Patel R. Mucormycosis and entomophthoromycosis: a review of the clinical manifestations, diagnosis and treatment. *Clin Microbiol Infect* 2004; 10: 31-47.
- [3] Vasaitis L. IgG4-related disease: a relatively new concept for clinicians. *Eur J Intern Med* 2016; 27: 1-9.
- [4] Brito-Zerón P, Ramos-Casals M, Bosch X, Stone JH. The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014; 13: 1203-1210.
- [5] Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012; 22: 21-30.
- [6] Deshpande V, Zen Y, Chen JK, Yi EE, Sato Y, Yoshino T. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; 25: 1181-1192.
- [7] Inoue D, Zen Y, Abo H, Gabata T, Demachi H, Kobayashi T, Yoshikawa J, Miyayama S, Yasui M, Nakanuma Y, Matsui O. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. *Radiology* 2009; 251: 260-270.
- [8] Butala A, Shah B, Cho YT, Schmidt MF. Isolated pulmonary mucormycosis in an apparently normal host: a case report. *J Natl Med Assoc* 1995; 87: 572-574.
- [9] Acharya S, Shukla S, Noman O, Dawande P. Isolated pulmonary mucormycosis presenting as cavitary lesion in an immunocompetent adult: a rare case report. *Int J Appl Basic Med Res* 2016; 6: 73-74.
- [10] Afolayan O, Copeland H, Hargrove R, Zaheer S, Wallen JM. Successful treatment of invasive pulmonary mucormycosis in an immunocompromised patient. *Ann Thorac Surg* 2016; 101: e117-119.
- [11] Rammaert B, Lanternier F, Zahar JR, Dannaoui E, Bournoux ME, Lecuit M, Lortholary O. Healthcare-associated mucormycosis. *Clin Infect Dis* 2012; 54: 44-54.
- [12] Choo JY, Park CM, Lee HJ, Lee CH, Goo JM, Im JG. Sequential morphological changes in follow-up CT of pulmonary mucormycosis. *Diagn Interv Radiol* 2014; 20: 42-46.
- [13] Lee FY, Mossad SB, Adal KA. Pulmonary mucormycosis: the last 30 years. *Arch Intern Med* 1999; 159: 1301-1309.
- [14] Jung J, Kim MY, Lee HJ, Park YS, Lee SO, Choi SH, Kim YS, Woo JH, Kim SH. Comparison of computed tomographic findings in pulmonary mucormycosis and invasive pulmonary aspergillosis. *Clin Microbiol Infect* 2015; 21: e11-18.
- [15] Gupta V, Rajagopalan N, Patil M, Shivaprasad C. Aspergillus and mucormycosis presenting with normal chest X-ray in an immunocompromised host. *BMJ Case Rep* 2014; 2014: bcr2014204022.
- [16] Aithal GP, Breslin NP, Gumustop B. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; 345: 147-148.
- [17] Guma M, Firestein GS. IgG4-related diseases. *Best Pract Res Clin Rheumatol* 2012; 26: 425-438.
- [18] Pifferi M, Di Cicco M, Bush A, Caramella D, Chilosi M, Boner AL. Uncommon pulmonary presentation of IgG 4-related disease in a 15-year-old boy. *Chest* 2013; 144: 669-671.
- [19] Sekiguchi H, Horie R, Utz JP, Ryu JH. IgG4-related systemic disease presenting with lung entrapment and constrictive pericarditis. *Chest* 2012; 142: 781-783.
- [20] Tanaka K, Nagata K, Tomii K, Imai Y. A case of isolated IgG4-related interstitial pneumonia. *Chest* 2012; 142: 228-230.
- [21] Sprangers B, Lioen P, Meijers B, Lerut E, Meerschaert J, Blockmans D, Claes K. IgG4-associated pulmonary-renal disease. *Chest* 2011; 140: 791-794.
- [22] Iwasaki T, Tachibana I, Yoshida S, Shimazu K, Takeda Y, Nagano H, Kawase I. A 61-year-old man with a lung nodule and elevated serum IgG. *Chest* 2010; 137: 1232-1235.