

The confused puzzles in ANCA-associated vasculitis activity evaluation:a case report

Ai-hua Zhang¹, Wei-long Yao¹, and Wen-hu Liu¹

¹Capital Medical University Affiliated Beijing Friendship Hospital

May 8, 2021

Abstract

Disease activity and treatment-related toxicity are the most important contributors to poor prognosis in patients with ANCA-associated vasculitis (AAV). Sometimes, it is difficult to distinguish them. We present a case to highlight the challenges in the management of AAV and the complications with immunosuppression.

TITLE

The confused puzzles in ANCA-associated vasculitis activity evaluation:a case report

Running Head

Puzzling ANCA-associated vasculitis activity

AUTHORS

Ai-hua Zhang¹, Wei-long Yao, Wen-hu Liu

ADDRESS

Department of Nephrology, Affiliated Beijing Friendship Hospital

Nephrology Faculty,

Capital Medical University,

No. 95 Yong An Road, Xi Cheng District,

Beijing 100050, the Peoples Republic of China

Telephone Number: +86-10-63138579

Fax Number: +86-10-63139144

E-mail: z15210076255@163.com

Corresponding author:

Department of Nephrology, Affiliated Beijing Friendship Hospital

Nephrology Faculty,

Capital Medical University

Beijing 100050, Peoples Republic of China.

Tel.: +86-10 63138579; fax: +86-10 63139144.

E-mail address: z15210076255@163.com

Abstract

Background

Disease activity and treatment-related toxicity are the most important contributors to poor prognosis in patients with ANCA-associated vasculitis (AAV). Sometimes, it is difficult to distinguish them. We present a case to highlight the challenges in the management of AAV and the complications with immunosuppression.

Case presentation

An 81-year-old female patient presented to our institution with gross hematuria, fatigue, nausea, anorexia, and progressively deteriorating renal function. ANCA enzyme immunoassay revealed a perinuclear staining pattern (p-ANCA) and serum anti-myeloperoxidase (MPO) antibody titer of 119 units/ml. She initially improved with intravenous methylprednisolone. However, after tapering the glucocorticoids and starting cyclophosphamide, her appetite and general state worsened, with increased body temperature, but serum creatinine and C-reactive protein concentrations and the erythrocyte sedimentation rate keep being decreased. Intravenous immunoglobulin and antibiotics had no effect. Intensive immunosuppressive therapy was initiated, and just as she improved, she suddenly developed purulent and blood-tinged sputum. Computed tomography of the chest showed a solid nodule with cavitation in the dorsal segment of the left lower lobe. Sputum culture revealed growth of *Mucor* species. Amphotericin B liposomes (LAMB) were administered, and the cumulative dosage was 2.0 g with 2 months' treatment duration. Finally, repeat sputum culture was negative, the nodular lesion disappeared, and only a cystic air space remained. No nephrotoxicity with LAMB was seen.

Conclusions

Comprehensive dynamic evaluation is important for patients with AAV. The subjective symptoms and objective indicators are not fully parallel, and manifestations between disease activity and treatment-related adverse reactions are often similar.

Key words

ANCA-associated vasculitis, immunosuppressive therapy, disease activity, adverse effect, infection, mucormycosis

Background

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of chronic multisystem autoimmune diseases with substantial mortality and morbidity and frequent relapses. AAV is characterized by predominant small vessel inflammation and necrosis in conjunction with ANCA in 60%–90% of cases at disease onset. With the introduction of treatment with corticosteroids and immunosuppressant drugs, the remission rate has improved in most cases, but patients with AAV are still at increased risk of death compared with age- and sex-matched members of the general population^[1]. Infection plays a critical role in these patients' adverse outcomes^[2]. Approximately 20%–60% of patients with AAV develop infections^[3], and severe infections are associated with permanent organ damage and high mortality. Opportunistic viral infections, such as cytomegalovirus (CMV) infection, herpes zoster (HZ), and fungal or bacterial infections, can be seen in patients with AAV^[3].

Moreover, the complexity of the disease condition and other treatment-related adverse reactions as well as infections are often confusing. Frequently, it is difficult to distinguish them because of their similar manifestations. Here, we describe a case of pulmonary mucormycosis in an old female patient with AAV to highlight these challenges.

Case presentation

An 81-year-old female patient with a 5-year history of microscopic hematuria presented to our institution in May 2017 with complaints of gross hematuria and fatigue persisting for 2 months, and nausea and anorexia persisting for 10 days, but with no fever, edema, oliguria, weight loss, or hemoptysis. She had a history of diabetes mellitus for 20 years and a history of hypertension for 9 years.

Physical examination revealed blood pressure (BP) at 120/80 mmHg, normal sinus rhythm, moderate anemic appearance, and moist rales in her left lower lung. Laboratory results indicated rapidly progressive deterioration of renal function. Serum creatinine (SCr) was 97.6 $\mu\text{mol/L}$ on February 21, 254.2 $\mu\text{mol/L}$ on April 28, and 276.1 $\mu\text{mol/L}$ on May 2, 2017 (range: 41–111 $\mu\text{mol/L}$). Urinalysis showed 3+ blood, 2+ protein, and full-visual-field red blood cells (RBCs) per high-power field with 60% dysmorphic RBCs. Serum albumin was 38.4 g/L, and 24-hour urinary protein quantitation was 4.26 g. Hemoglobin (Hb) was 76 g/L, the white blood cell count (WBC) was $7.54 \times 10^9/\text{L}$, platelet count (PLT) was $177 \times 10^9/\text{L}$, and erythrocyte sedimentation rate (ESR) was 69 mm/h (range: 0–15 mm/h). The concentrations of plasma C3 (54.1 mg/dl) and C4 (1.56 mg/dl) were significantly reduced (range: 90–180 mg/dl and 10–40 mg/dl, respectively). Anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-Smith (anti-Sm), anti-Sjogren syndrome A antibody (anti-SSA), and anti-Sjogren syndrome B (anti-SSB) antibodies were all negative with weakly positive antinuclear antibody (1:160). Test results for rheumatoid factor, C-reactive protein (CRP), and serum cryoglobulin were normal. ANCA enzyme immunoassay revealed a perinuclear staining pattern (p-ANCA) and serum anti-myeloperoxidase (MPO) antibody of 119 units/ml (normal: < 20 U/ml), whereas anti-protease 3 and serum anti-glomerular basement membrane antibody concentrations were normal. The results of infectious studies for hepatitis C (HCV), hepatitis B (HBV), and human immunodeficiency virus (HIV) were negative. Renal ultrasonography showed normally-sized kidneys and increased cortical echogenicity. Chest computed tomography (CT) indicated a small nodule in the superior lobe of the right lung and a ground-glass opacity nodule in the superior lobe of the left lung (Fig. 1).

We diagnosed AAV; renal biopsy was not performed because the patient declined this procedure.

The First Stage

On the first day of hospitalization (May 4), intravenous methylprednisolone (40 mg) was administered. SCr continued to increase to 319 $\mu\text{mol/L}$ the following day (May 5). From May 5 through 7 (3 days), a higher dose of methylprednisolone (80 mg per day) was used. The patient felt better, with improved appetite and urine color. The therapy was adjusted to intravenous methylprednisolone (40 mg per day) and a regimen of intravenous cyclophosphamide (CTX) at a fixed dose of 400 mg on 2 consecutive days (May 8 and 9).

The Second Stage

From May 8, her appetite and general state worsened again with frequent nausea and fatigue, but still with no fever, cough, expectoration, or hemoptysis. Most laboratory indices were improving except for plasma complement levels (C3: 53.6 mg/dl and C4: 1.66 mg/dl). The SCr concentration decreased to 241.6 $\mu\text{mol/L}$, ESR was 16 mm/h, and the CRP concentration was normal. Owing to the development of leukopenia, the discordance between the patient's subjective symptoms and objective indicators was initially interpreted as a possible adverse reaction to the CTX, and CTX was discontinued. Nevertheless, her condition continued to worsen. On May 12, she developed dark urine again and a fever, with a temperature as high as 38.5°C. The moist rales in both lung bases worsened significantly, with increased patchy shadows on chest X-rays (Fig. 2). SCr continued to decrease (226.9 $\mu\text{mol/L}$), which was also confusing, and there was minimal evidence of infectious complications, with normal CRP and procalcitonin concentrations. Intravenous immunoglobulin (IVIG) was prescribed (20 g per day, for 5 days). However, there was no clinical response, and her fever increased to 39°C; antibiotics were re-prescribed (cefoperazone-sulbactam 0.5 g every 12 hours for 3 days, followed by meropenem 0.25 g every 12 hours). In the absence of immediate improvement, ANCA was reanalyzed. The MPO antibody concentration had increased to 136.9 units/ml, and the methylprednisolone dosage was increased to 80 mg per day again. Unfortunately, the patient showed no improvement, with a continuous fever, decreased urine volume (approximately 600 ml per day), and exacerbated renal function (SCr: 408.7 $\mu\text{mol/L}$ on May 17). Peripheral blood (1-3)- β -D-glucan, cytomegalovirus DNA, and *Pneumocystis carinii*

antigen and antibody were all negative. Dialysis was initiated with high-dose intravenous methylprednisolone pulse therapy (320 mg per day for 3 days, followed by 40 mg per day). Five days later (May 22), her temperature returned to normal with decreased MPO antibody concentration (86.3 units/ml) and improved urine color. Although the plasma C4 concentration improved (3.11 mg/dl), C3 concentrations decreased further (36.3 mg/dl), and her urine volume showed no significant increase. All of these findings implied on-going disease activity. According to the leukopenia and for economic reasons, cyclosporine A (CsA) was added to the glucocorticoids, with a plasma concentration of 80–90 ng/ml. The patient's alimentary symptoms and fatigue decreased in response to this therapy.

The Third Stage

On May 29, the patient suddenly developed purulent and blood-tinged sputum without fever or dyspnea. Urine volume reached 1500 ml with diuretics, urine color was normal, and SCr before dialysis was 211 $\mu\text{mol/L}$. ESR and serum CRP were normal. Although p-ANCA was still positive with an immunofluorescent technique, MPO antibody concentration was already below 20 units/ml. Plasma C3 and C4 concentrations were unchanged, and both serum procalcitonin and the T-SPOT.TB test were negative. Chest X-rays revealed no specific findings (Fig. 3). One day later, sputum culture revealed growth of *Mucor* species, and the serum (1-3)- β -D-glucan concentration had increased to 504.2 pg/ml. Chest CT was repeated and showed a solid nodule with cavitation in the dorsal segment of the left lower lobe (Fig. 4). In light of the improvement in the other activity indicators, pulmonary mucormycosis was believed to be present rather than contamination, although the sputum sample was not obtained using bronchoscopy. According to the drug sensitivity testing results, amphotericin B liposomes (LAMB) were administered intravenously. The initial dosage was 10 mg per day (May 30), and the dose was increased by 5 mg every other day to 50 mg per day. The cumulative dosage was 2.0 g, with 2 months' treatment duration. In the first 3 days, cetirizine and acetaminophen were used to prevent allergic reactions. The treatment protocol was well tolerated, and the patient expressed no discomfort, such as shivering, fever, or arthralgia. By June 4 (5 days later), the expectoration had resolved. Two weeks later (June 12), chest CT revealed that the cavitary wall had thinned significantly although the lesion's extent appeared wider (Fig. 5). Four weeks later (June 27), the lung lesion and its internal cavity had shrunk (Fig. 6). At the end of treatment, sputum culture was negative, the nodular lesion had disappeared, and only a cystic air space remained (Fig. 7). No LAMB-related nephrotoxicity was seen. On July 28, dialysis was withdrawn; urine volume was normal, and SCr was 133.9 $\mu\text{mol/L}$. However, plasma C3 and C4 concentrations remained low (32.6 mg/dl and 1.56 mg/dl, respectively). The patient was discharged from hospital with 20 mg prednisone per day and 75 mg CsA twice a day.

Discussion and Conclusion

Mucormycosis is a rare, highly aggressive, and usually fatal infection^[4], which in humans is mainly limited to hosts with risk factors, such as hematologic diseases, organ transplantation, severe immunosuppression, diabetes mellitus, renal failure, solid tumors, and malnutrition^[5-6]. The clinical forms may be cutaneous, rhinocerebral, pulmonary, and disseminated infections^[5,7]. Our patient had several risk factors (diabetes mellitus, progressive renal dysfunction, and immunosuppressive treatment); however, few patients with AAV have been reported with acquired *Mucor* species infections. Treatment-related factors might have played an important role in our patient's clinical course. First, given her age, we hoped to use lower doses of corticosteroids to control disease activity, initially^[8]. Her symptoms improved after 80 mg/d methylprednisolone for 3 days, and the dosage was decreased by half with intravenous CTX. This tapering regimen was hasty, which might have contributed to her disease relapse, resulting in a larger cumulative dose and longer exposure time. Second, the CTX dosage was higher than the recommended guidelines. The latest kidney disease improving global outcomes (KDIGO) guideline draft suggests an intravenous dose of CTX of 10 mg/kg for 70-year-old patients at weeks 0, 2, 4, 7, 10, and 13. Therefore, 600 mg CTX may be more appropriate than 400 mg for 2 consecutive days. On May 27, leukopenia occurred (peripheral blood leukocyte count: $3.26 \times 10^9/\text{L}$), and the lymphocyte absolute value was $0.34 \times 10^9/\text{L}$, in which the cluster of differentiation 4 (CD4) cell count was less than 50/ μl . These findings were associated with the *Mucor* species infection. Garcia-Vives, et al.^[9]

retrospectively analyzed 132 AAV patients and found that leukopenia was the only factor independently related to opportunistic infections. Third, broad-spectrum antibiotic use also increased the risk of fungal infection. Although trimethoprim-sulfamethoxazole and acyclovir can be used to prevent *Pneumocystis carinii* pneumonia and cytomegalovirus infection, respectively, in immunocompromised patients, there are no effective preventive measures for deep fungal infections. Our patient received nystatin gargling twice a day, which failed to prevent fungal infection. *Mucor* species are widely distributed in nature; intensive air purification might be helpful.

Lin et al.^[10] retrospectively reviewed the clinical data of 35 patients with pulmonary mucormycosis. The authors reported that common presenting clinical findings were fever, neutropenia, dyspnea, and cough, and that the radiologic findings were pleural effusion and nodules. Our patient had an emerging pulmonary nodule, but no fever or dyspnea, which might have resulted from the use of CsA.

Calcineurin plays essential roles in the virulence and growth of pathogenic fungi^[11]. Calcineurin mutation or inhibition confers a yeast-locked phenotype that is vulnerable to control by host macrophages. Additionally, concurrent bacteremia is the sole reported independent predictor of mortality^[10]. Owing to antibiotic use, our patient did not develop bacterial infections; and in this sense, antibiotics may have been a double-edged sword.

Hemoptysis is related to the invasion of vessel walls by *Mucor* species^[5]. One study reported that mucormycosis could cause arterial thrombosis and thrombotic microangiopathy^[12]. Vasculitis can also lead to pulmonary nodules and hemoptysis; hence, distinguishing between infection and disease activity is essential. However, the early diagnosis of pulmonary mucormycosis is difficult^[13]. With a high level of suspicion, chest CT is more useful than plain X-rays. Monitoring galactomannoglycan (GM), and polymerase chain reaction (PCR) and antibody testing may also be helpful^[5]. Finally, clinicians should remain vigilant in high-risk patients.

Initially, with our patient, the paradoxical subjective symptoms and objective indicators were confusing. On the first day of hospitalization, the patient's Birmingham vasculitis activity score (BVAS)^[14] was 16 compared with 10 after the CTX infusion, which suggested that AAV disease activity had decreased. However, the patient's later condition revealed that this was not the case. BVAS may be more often used to assess the disease activity at diagnosis^[2]. In our patient, SCr increase fell behind symptom deterioration for several days. Therefore, the combined dynamic assessments of symptoms, signs, and additional examinations are more important than individual indices, especially during immunosuppressive treatment. Indeed, it was a limitation that kidney biopsy was not obtained, in this case.

This patient had significant hypocomplementemia. In the past decade, several studies have suggested that the complement system is involved in the pathogenesis of AAV^[15]. However, nearly all evidence suggests an alternative pathway^[15-16]. Plasma C3 and C4 concentrations were both obviously decreased in this patient. Although the role of C4 remains to be researched, a retrospective cohort study has shown that patients with low C3 or C4 experienced increased renal damage^[17]. Hypocomplementemia may be involved in our patient's protracted disease course and in developing the opportunistic infection.

Disease activity and treatment-related toxicity are the most important prognostic factors for patients with AAV. However, their clinical manifestations are often very confusing, and it is a great challenge for physicians to distinguish uncontrolled disease from treatment-related complications. Constant alertness and vigilance are needed during the entire treatment course.

Abbreviations

ANCA: antineutrophil cytoplasmic antibody; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; CMV: cytomegalovirus; HZ: herpes zoster; BP: blood pressure; SCr: serum creatinine; RBC: red blood cell; Hb: hemoglobin; WBC: white blood cell; PLT: platelet; ESR: erythrocyte sedimentation rate; anti-dsDNA: anti-double-stranded deoxyribonucleic acid antibody; anti-Sm: anti-Smith antibody; anti-SSA: anti-Sjogren syndrome A antibody; anti-SSB: anti-Sjogren syndrome B antibody; CRP: C-reactive protein; p-

ANCA: perinuclear antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; HCV: hepatitis C; HBV: hepatitis B; HIV: human immunodeficiency virus; CT: computed tomography; CTX: cyclophosphamide; IVIG: intravenous immunoglobulin; CsA: cyclosporine A; T-SPOT.TB: T-cell SPOT *Tuberculosis* bacillus; LAMB: amphotericin B liposomes; KDIGO: kidney disease improving global outcomes; CD4: cluster of differentiation 4; GM: galactomannoglycan; PCR: polymerase chain reaction; BVAS: Birmingham vasculitis activity score.

Declarations

Funding

All authors state that there was no funding for this work.

Availability of data and material

The datasets supporting the conclusions of this article are included within the article and additional files. The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable. This type of study does not require approval by our EthicsCommittee.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the study conception and design. YW collected the clinical data. ZA was a major contributor in writing the manuscript. Writing: review and editing were performed by LW.

Acknowledgment

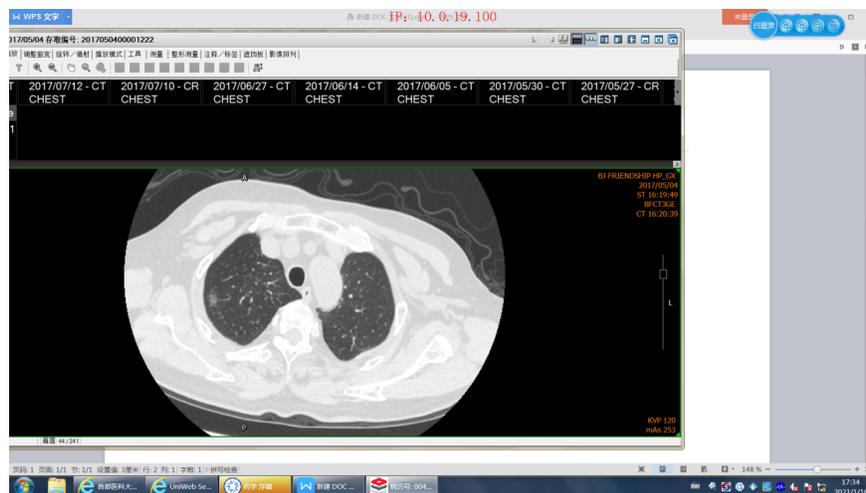
We thank Jane Charbonneau, DVM, from Liwen Bianji, Edanz Group China (<http://www.liwenbianji.cn/ac>), for editing the English text of a draft of this manuscript.

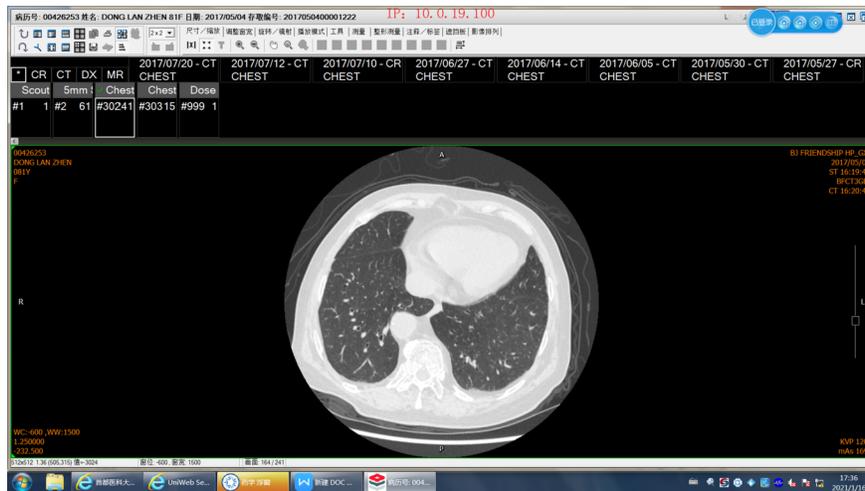
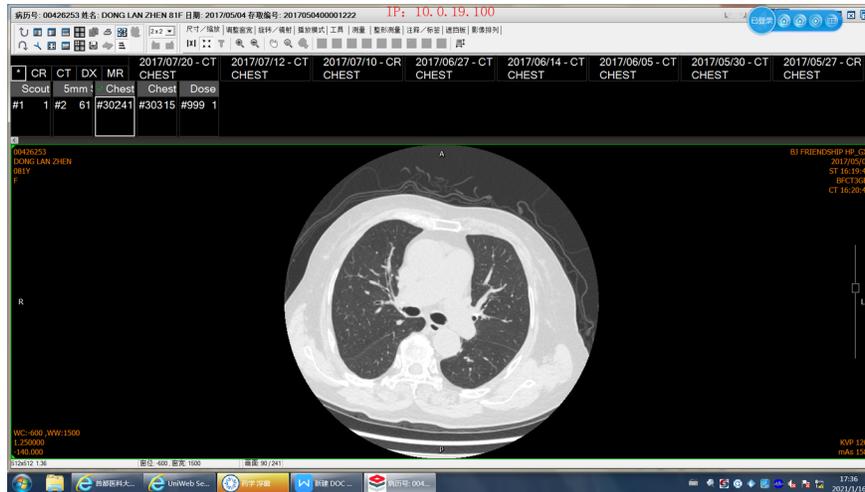
References

1. Tocut M, Rozman Z, Biro A, et al. Comparison of the Birmingham Vasculitis Activity Score and the Five-Factor Score to assess survival in antineutrophil cytoplasmic antibody-associated vasculitis: a study of 550 patients from Spain (REVAS Registry). *Arthritis Care Res (Hoboken)*. 2020;72(7):1001-1010.
2. Rathmann J, Jayne D, Segelmark M, et al. Incidence and predictors of severe infections in ANCA-associated vasculitis: a population-based cohort study. *Rheumatology (Oxford)*. 2020 Nov 30; keaa699.
3. Sakai R, Tanaka E, Nishina H, et al. Risk of opportunistic infections in patients with antineutrophil cytoplasmic antibody-associated vasculitis, using a Japanese health insurance database. *Int J Rheum Dis* . 2019;22(11):1978-1984.
4. Konigsberg MW, Wu CH, Strauch RJ. Topical treatment for cutaneous mucormycosis of the upper extremity. *J Hand Surg Am*. 2020;45(12):1189.e1-1189.e5.
5. Zhan HX, Lv Y, Zhang Y, et al. Hepatic and renal artery rupture due to *Aspergillus* and *Mucor* mixed infection after combined liver and kidney transplantation: a case report. *Transplant Proc* . 2008;40(5):1771-1773.
6. Paul SR, Gable PS. Mucormycosis as the elusive cause of an aortic thrombus and tissue-obliterating abscess. *Case Rep Hematol*. 2019:4842150.

- Godara SM, Kute VB, Goplani KR, et al. Mucormycosis in renal transplant recipients: predictors and outcome. *Saudi J Kidney Dis Transpl.* 2011;22(4):751-756.
- Waki D, Nishimura K, Tokumasu H, et al. Initial high-dose corticosteroids and renal impairment are risk factors for early severe infections in elderly patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: A retrospective observational study. *Medicine (Baltimore).* 2020;99(8):e19173.
- Garcia-Vives E, Segarra-Medrano A, Martinez-Valle F, et al. Prevalence and risk factors for major infections in patients with antineutrophil cytoplasmic antibody-associated vasculitis: influence on the disease outcome. *J Rheumatol.* 2020;47(3):407-414.
- Lin E, Moua T, Limper AH. Pulmonary mucormycosis: clinical features and outcomes. *Infection.* 2017;45(4):443-448.
- Lee SC, Li A, Calo S, et al. Calcineurin orchestrates dimorphic transitions, antifungal drug responses and host-pathogen interactions of the pathogenic mucoralean fungus *Mucor circinelloides*. *Mol Microbiol.* 2015;97(5):844-865.
- Inagaki N, Sugimoto K, Hosone M, et al. Disseminated Mucor infection and thrombotic microangiopathy in lymphoma-associated hemophagocytic syndrome. *Int J Hematol.* 2008;88(3):355-356.
- Santos Silva J, Torres C, Clemente S, et al. Isolated Pulmonary Mucormycosis in an immunocompetent patient. *Rev Port Cir Cardiorac Vasc.* 2019;26(2):151-153.
- Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis.* 2009;68(12):1827-1832.
- Chen M, Jayne DRW, Zhao MH. Complement in ANCA-associated vasculitis mechanisms and implications for management. *Nat Rev Nephrol.* 2017;13(6):359-367.
- KaKallenberg CG, Heeringa P. Complement system activation in ANCA vasculitis: A translational success story? *Mol Immunol.* 2015;68(1):53-56.
- García L, Pena CE, Maldonado RÁ, et al. Increased renal damage in hypocomplementemic patients with ANCA-associated vasculitis: retrospective cohort study. *Clin Rheumatol.* 2019;38(10):2819-2824.

Fig. 1 Chest CT scan of the patient on May 4, 2017.





It indicated a small nodule in the superior lobe of the right lung and a ground-glass opacity nodule in the superior lobe of the left lung.

Fig. 2 Chest X-ray plain on May 12, 2017.



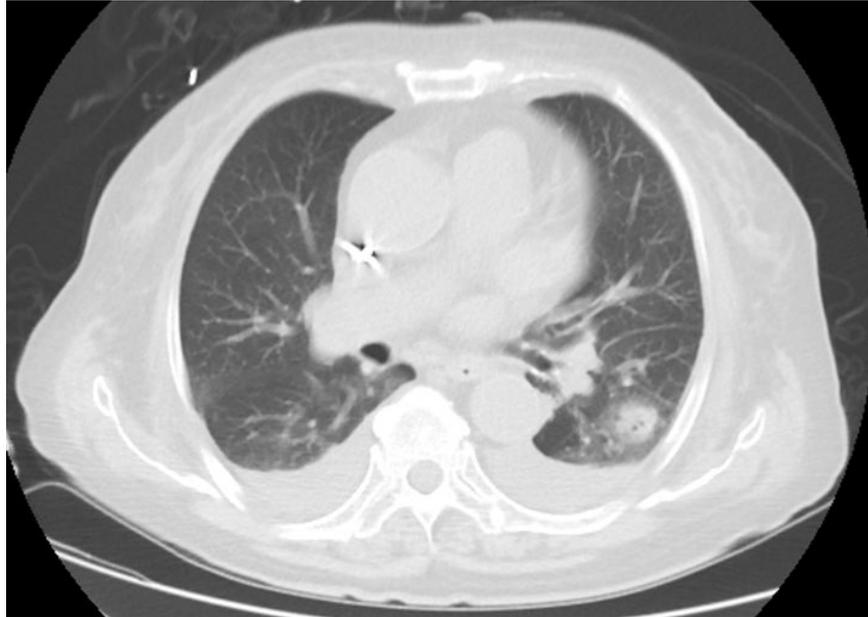
The moist rales in both lung bases worsened significantly, with increased patchy shadows.

Fig. 3 Chest X-ray plain on May 29, 2017.



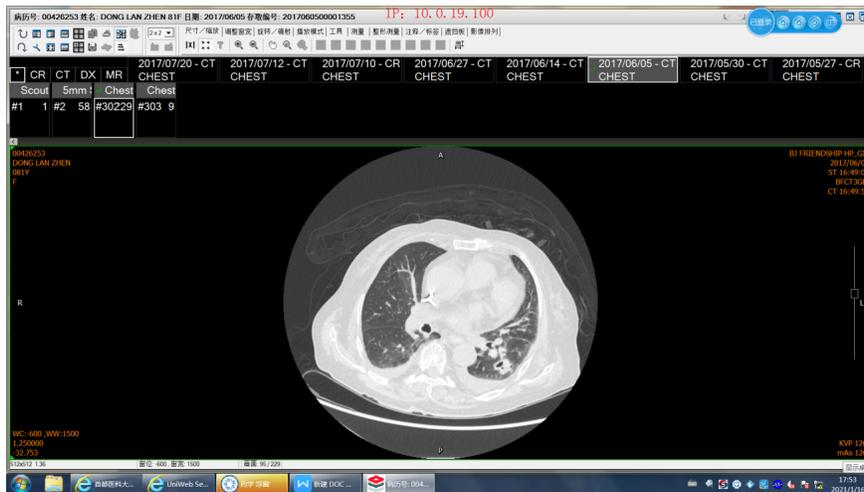
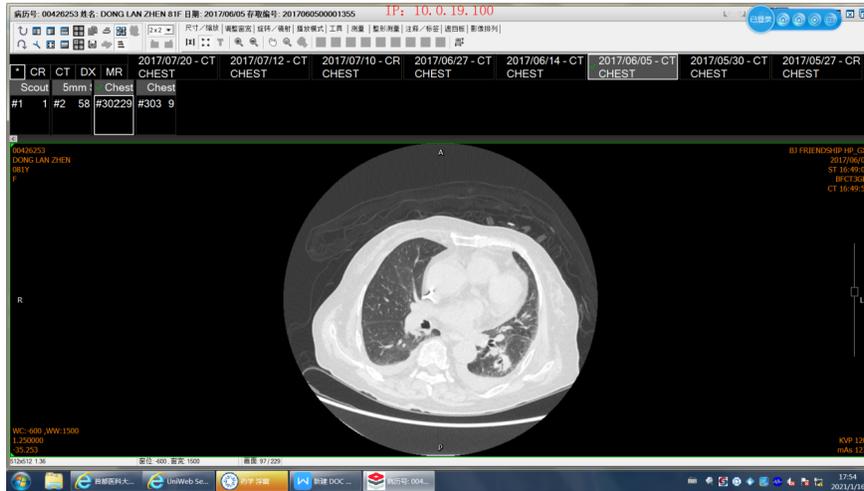
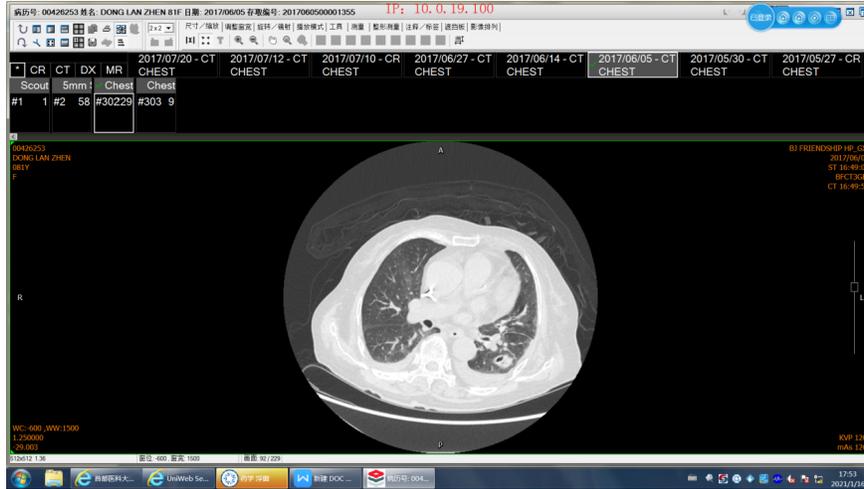
Chest X-rays revealed no specific findings.

Fig. 4 Chest CT scan on May 30, 2017.



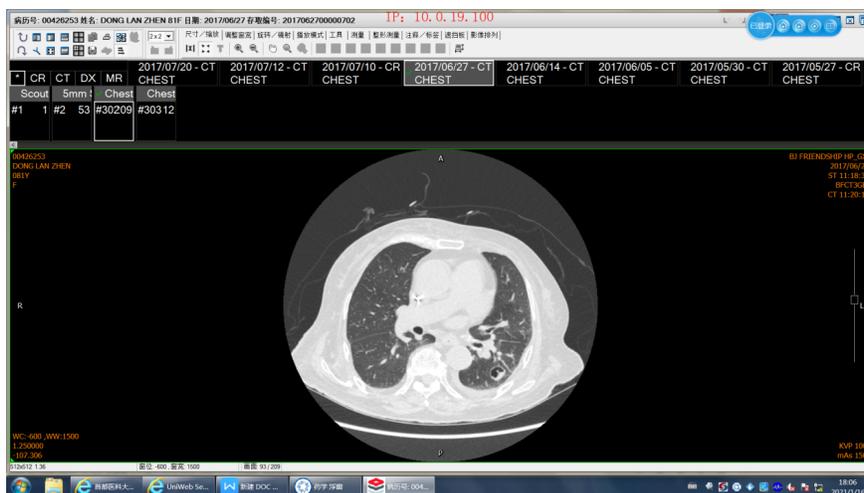
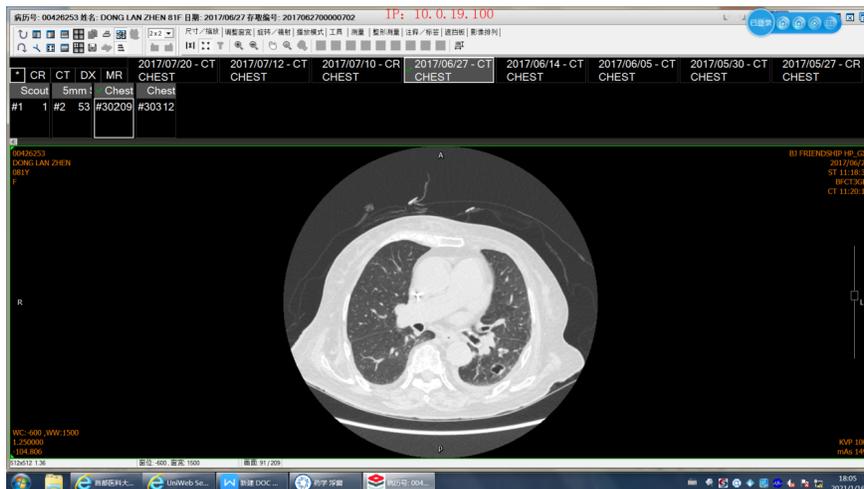
Chest CT showed a solid nodule with cavitation in the dorsal segment of the left lower lobe.

Fig. 5 Chest CT scan on June 12, 2017.



Two weeks later, the cavitory wall had thinned significantly although the lesion's extent appeared wider.

Fig. 6 Chest CT scan on June 27, 2017.





Four weeks later, the lung lesion and its internal cavity had shrunk.

Fig. 7 Chest CT scan on July 20, 2017.





At the end of treatment, sputum culture was negative, the nodular lesion had disappeared, and only a cystic air space remained.