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CASE REPORT

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Chronic pulmonary Aspergillosis in a patient with poorly controlled diabetes: A case report and literatures review

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Abstract

Chronic pulmonary aspergillosis (CPA) often manifests in patients with a history of pulmonary tuberculosis and is typically characterized by recurrent hemoptysis, weight loss, and frequently coexists with poorly controlled diabetes. While weight gain is acknowledged as a valuable clinical marker for monitoring therapeutic responses in CPA, there is a scarcity of case reports exploring this aspect. Furthermore, the impact of stringent blood sugar management in diminishing CPA activity and preventing the recurrence of hemoptysis is also underreported. In this context, we present the case of a 64-year-old male who experienced massive hemoptysis. He had a background of uncontrolled diabetes and a history of fully treated pulmonary tuberculosis. Following therapeutic embolization, he was diagnosed with CPA that had transformed into invasive pulmonary aspergillosis (IPA) and underwent antifungal therapy for 9 months. Notably, we observed an inverse correlation between the patient's improved blood sugar control and weight gain with the serum IgG levels for Aspergillosis. This case highlights the potential benefits of non-invasive monitoring of CPA activity and the identification of treatment responders through effective blood sugar management and weight gain.

KEYWORDS
chronic pulmonary aspergillosis, diabetes mellitus

INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is a progressive respiratory syndrome predominantly affecting individuals who are immunocompetent or subtly immunocompromised, particularly those with underlying structural lung diseases, most notably post-treatment tuberculosis (TB).[1] In recent years, it has become an increasingly important global public health concern.[1,2] As per the recommendations by the European Confederation of Medical Mycology (ECMM), indicators for monitoring CPA include imaging assessment, culture from respiratory samples, and serology on *Aspergillus*-specific IgG.[3] Some studies, on the other hand, suggested only a weak correlation between serology finding and CPA treatment.[4] Furthermore, advanced imaging tools such as CT scans and FDG-PET/CT scans, along with *Aspergillus*-specific IgG, are expensive and not practically accessible in developing countries. This emphasizes the importance of developing reliable and non-invasive assessment indicators for such patients.

Recent studies have underscored a potential link between weight gain and improvements in both radiological findings and symptoms in CPA patients.[5–7] Notably, weight gain has been identified as a clinical indicator for monitoring therapeutic responses in CPA cases.[8] Sehgal et al. also observed that significant weight gain at 6 months, compared to baseline measurements, correlated with positive treatment responses, while substantial weight loss may indicate therapy failure.[4] Despite these findings, no case reports have specifically addressed this correlation to date. Moreover, while diabetes is recognized as a risk factor for both CPA and invasive pulmonary aspergillosis (IPA),[9,10] the impact of strict blood sugar control on reducing CPA activity and preventing hemoptysis recurrence remains unclear.

In this report, we present a complex case involving poorly controlled diabetes that manifested as massive hemoptysis due to IPA, a consequence of CPA transformation. Interestingly, the patient's improved blood sugar control and weight gain inversely correlated with serum IgG levels for Aspergillosis. This case also illustrates the potential for non-invasive monitoring of CPA activity and identifying treatment responders through improved blood sugar management and weight gain.

CASE REPORT

A 64-year-old male presented with hemoptysis for 3 days, along with fever, body weight loss, and generalized malaise for the past 3 weeks, prompting him to seek medical help.

He was a former smoker of 40 years, with a history of pulmonary tuberculosis (PTB) 20 months prior this admission. He was enrolled in routine follow-up at a DOTS clinic and received regimen included Rifampin (RMP), Isoniazid (INH), Pyrazinamide (PZA), and Ethambutol (EMB) for the initial 2 months, followed by a 4-month continuation phase (INH and RMP). Over the subsequent 6 months of treatment, three consecutive sputum mycobacterial cultures yielded no bacterial growth at monthly intervals, fulfilling the IDSA-defined criteria for completion of therapy.[11] He was diagnosed with type 2 diabetes mellitus 2 years prior, presenting with an initial HbA1c level of 13%. His diabetes has been managed with metformin, dosed at 500 mg orally twice daily. The most recent measurement showed his HbA1c level at 9.0%.

On arrival of emergency department, his chest x-ray demonstrated alveolar pattern in the left upper lung lobe with multiple satellite lesions. On the day of admission, despite the use of tranexamic acid 1 g intravenously (IV), every 6 h, and ampicillin/sulbactam 1 or 0.5 g IV, every 6 h, hemoptysis persisted. On day 5 of admission, he developed massive hemoptysis, leading to hypo-volemic shock and cardiac arrest. He received 15 min of cardiopulmonary resuscitation before spontaneous circulation returned. He was subsequently transferred to the intensive care unit (ICU).

Diagnostic assessments

Computed tomography angiography (CTA) was performed immediately, which revealed reticular pattern of fibrotic change surrounding multiple cavitated nodules and areas of consolidation in the left upper lobe. Besides, involved region also demonstrated tree-in-bud, consolidation and abundant blood supply. We obtained his blood cultures, sputum AFS, and sputum *Mycobacterium* cultures. On day 10 of admission, he received bronchoscopy, and was given bronchoalveolar lavage (BAL). Results are summarized in Table 1.

Aspergillus galactomannan (GM) antigen derived from both serum and BAL fluid showed positive results (0.451 and 2.983, respectively). Serum levels of IGA to *Aspergillus*

TABLE 1 Summary of microbiological findings and results.

Sample	Results (value)	Reference value
Pulmonary TB		
Sputum AFS (1st set)	Negative	Negative
Mycobacterium culture (1st set)	Negative	Negative
Sputum AFS (2nd set)	Negative	Negative
Mycobacterium culture (2nd set)	Negative	Negative
Sputum AFS (3rd set)	Positive (1+)	Negative
Mycobacterium culture (3rd set)	Negative	Negative
Sputum NAA test	Negative	Negative
Pulmonary aspergillosis		
Serum *Aspergillus* DNA PCR	Not detected	Not detected
Sputum *Aspergillus* DNA PCR	Positive (Ct: 30.04)	Not detected
BAL fluid *Aspergillus* DNA PCR	Positive (Ct: 28.91)	Not detected
Serum GM	Negative (Ratio = 0.451)	<0.5[a]
BAL fluid GM	Positive (Ratio = 2.983)	<0.7[a]
Specific IgE and IgG of *Aspergillus*		
A. fumigatus-IgG	Positive (77.2 mgA/L)	<41.6[b]
A. niger-IgG	Positive (70.0 mgA/L)	<40.8[b]
A. fumigatus-IgE	Negative (0.02 KU/L)	<0.06[b]
A. niger-IgE	Negative (0.01 KU/L)	<0.01[b]
BAL fluid microscopy	Positive for filament structure	Negative
BAL fungal culture	Negative for *Aspergillus* spp.	Negative
BAL NAA test	Negative	Negative
Pulmonary CMV		
BAL fluid viral culture	Negative	Negative
Others		
BAL fluid culture	*Klebiella pneumonia* *Candida tropicalis* *Candida albicans*	Negative
BAL fluid *Pneumocystis jirovecii*	Negative	Negative
BAL fluid *Legionella* DNA PCR	Negative	Negative
Mucorales DNA PCR	Negative	Negative
Chlamydia pneumoniae IgM	Negative	Negative
Urine *Legionella* antigen	Negative	Negative
Urine *Pneumococcus* antigen	Negative	Negative

Abbreviations: AFS, acid-fast stain; BAL, bronchoalveolar lavage; CMV, *cytomegalovirus*; GM, galactomannan; NAA, nucleic acid amplification; PCR, polymerase chain reaction; QPCR, quantitative polymerase chain reaction; TB, tuberculosis.

[a]Referenced from Zhou et al.[12]

[b]Referenced from Hsiao et al.[13]

fumigatus and *Aspergillus niger* were 77.2 and 70.0 mgA/L, respectively. Fungal DNA from PCR tests of sputum and BAL fluid had cycle threshold values of 30.04 and 28.91, respectively. Fungal culture of BAL fluid however did not yield any growth. Throughout his hospitalization, 4 sputum acid-fast staining (AFS) were collected, with only one giving trace positive finding. Nucleic acid amplification (NAA) test of tuberculosis from sputum and BAL fluid were all negative. None of any sputum samples yielded mycobacterium. Considering the patient's bronchoalveolar lavage (BAL) fluid yielded a positive galactomannan (GM) assay, positive Aspergillus DNA PCR, and filamentous structures observed via microscopic examination, these findings align with the criteria for a diagnosis of probable invasive pulmonary aspergillosis (IPA).[14] Additionally, the elevated levels of Aspergillus-specific IgG in this case led to a definitive diagnosis of CPA, which has subsequently transformed into IPA.

Intervention of massive pulmonary haemorrhage

On day 5 of admission, trans arterial embolization (TAE) was performed (Figure 1). Selective left 4th intercostal angiogram demonstrated tortuous intercostal artery and hyperperfusion involving the lung parenchyma; therefore, subsequent embolization with 350 μm EGgel Gelatin Microparticles (ENGAIN Company, Hwaseong, South Korea) was successfully performed. The bleeding condition gradually improved.

Following the embolization procedure, the patient was moved back to the Intensive Care Unit (ICU) for close observation. On admission to the ICU, he required intravenous fluid resuscitation and vasopressor support due to hypovolemic shock. From day 10, intravenous voriconazole (200 mg) was administered bi-daily as an antifungal treatment. Extubation was delayed initially due to a secondary pneumonia caused by a *Klebsiella pneumoniae* infection and resulting hypoxemia. When the patient's infection stabilized, a weaning protocol was initiated on day 18. Successful extubation of the endotracheal tube was achieved on day 20. Subsequently, the patient was discharged and continued with oral voriconazole therapy (200 mg daily) for an additional 9 months.

Follow-up and outcomes: managing blood sugar and CPA disease activity

Upon ICU admission, the patient's postprandial blood glucose levels were recorded between 200 and 300 mg/dL. To manage this, we started a regimen of long-acting insulin (degludec) once daily, complemented by short-acting insulin (aspart) before meals and at bedtime. Within 5 days, his postprandial glucose levels improved to 150–200 mg/dL, allowing us to transition him from insulin injections to oral antidiabetic medications, specifically Sitagliptin/Metformin (50/500 mg twice daily) and acarbose (100 mg twice daily). The patient also received comprehensive diabetes education and continued medication management, including Pioglitazone (30 mg daily) and Glimepiride (1 mg daily). We monitored his body weight and HbA1c levels quarterly. Notably, his condition of hemoptysis stabilized alongside controlled HbA1c levels and gradual weight gain (refer to Figure 2).

Regarding CPA activity, we conducted three Aspergillus-specific IgG tests, which showed levels of 77.2 mgA/L initially, increasing to 126 mgA/L by the fourth month, and then reducing to 79.7 mgA/L by the eighth month. Follow-up chest x-rays and CT scans showed resolution of the nodular lesions and ground-glass opacity (see Figure 3). As of the finalization of this article, the patient has experienced no recurrence of hemoptysis.

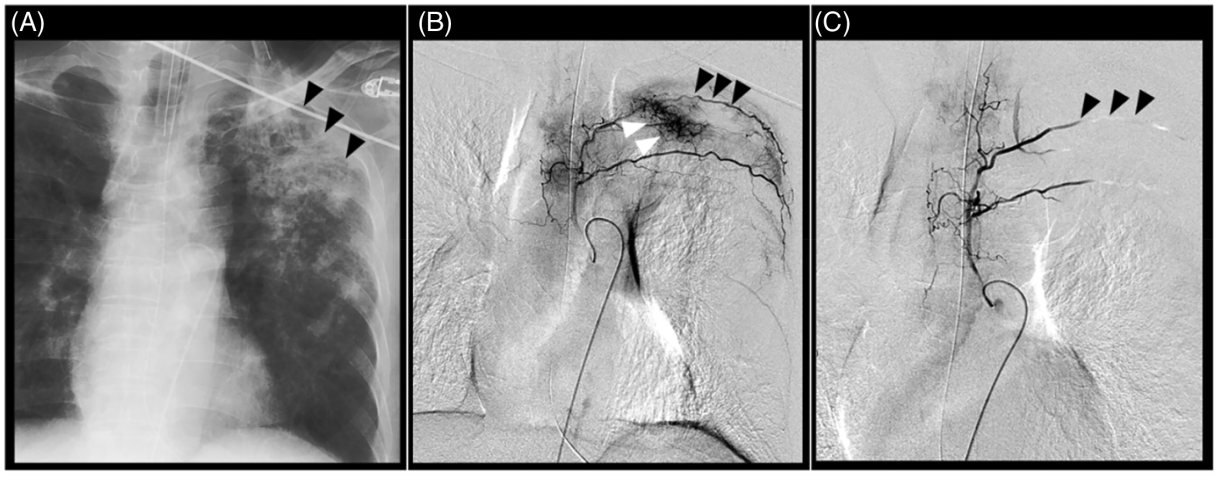

FIGURE 1 Digital subtraction angiography (DSA) of left intercostal arteries (GE Innova IGS5, GE Healthcare, Chicago, USA): (A) The pre-embolization plain film shows a destroyed lung in the left upper lobe (arrow in A). (B) Left 4th intercostal artery, with tortuous vessels branching from it and regional hypervascularity (black arrow), along with some contrast medium extravasation (white arrow). (C) The left 4th intercostal artery was successfully treated with 350um EGgel embolization (arrow in C).

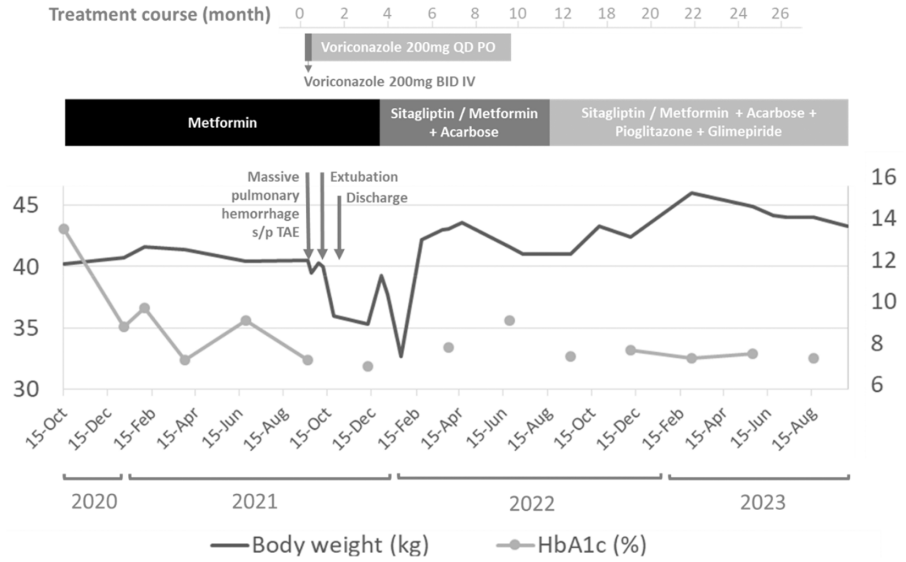

FIGURE 2 Weight (primary *y*-axis), HbA1c (secondary *y*-axis), and the timeline of clinical treatment. This timeline focuses on the relationship between HbA1c control and weight changes. It also illustrates the periods of use of antifungal drugs and antidiabetic agents. Month 0 of the treatment course is counted from the day of admission. BID, twice daily; IV, intravenous; PO, oral administration; QD, once daily; TAE, transarterial embolization.

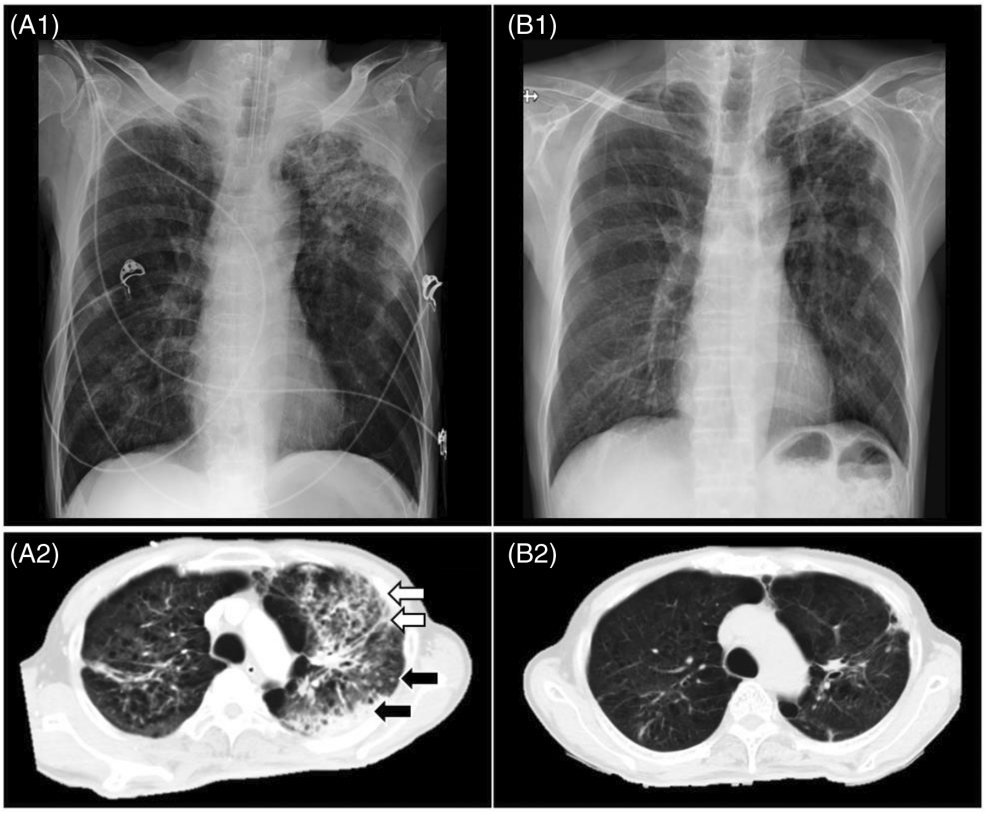

FIGURE 3 Demonstrates a series of CXR along with their corresponding CT scans, (A1–A2) baseline, and (B1–B2) after 9 months of anti-fungal treatment. (A1–A2) The white arrow indicates fibrosis and pleural thickening in the left upper lobe. The black arrow indicates perivascular tree-in-bud and consolidation, representing areas of active infection and abundant blood supply. (B1–B2) The consolidation and tree-in-bud lesions resolved, with some fibrotic scarring remaining. CT, computerized tomography; CXR, chest x-ray.

DISCUSSION

We present the case of a 64-year-old male with a history of uncontrolled diabetes and fully treated pulmonary tuberculosis, who experienced massive hemoptysis due to CPA with subsequent transformation into IPA. Following a nine-month course of antifungal treatment, the patient showed a favourable response, characterized not only by a

decrease in serum IgG levels for Aspergillosis and the absence of hemoptysis recurrence but also by improved blood sugar control and weight gain. This case underscores the potential advantages of non-invasive monitoring of CPA activity and the identification of treatment responders, emphasizing the role of effective blood sugar management and weight gain in patient outcomes.

The patient was diagnosed with CPA according to criteria published by ECMM, based on serum Aspergillus-specific IgG level and thoracic computed tomography imaging showing chronic fibrotic change after completion of antifungal treatment.[15] Aspergillus-specific IgG levels may vary across different patient populations. In this case report, the diagnostic threshold was based on that established in Taiwan in 2022.[12] Considering that only one set of sputum AFS showed positive results out of four and given the negative results of NAA test and sputum mycobacterial culture, we assumed that the positive AFS may indicate the presence of non-viable bacteria, particularly in this patient with a history of tuberculosis in the past. In addition, a comprehensive assessment of other comorbidities, including pulmonary TB co-infection,[16] bronchiectasis, and rupture of Rasmussen's aneurysm, is crucial. It is recommended to conduct a thorough search for as many culprit vessels as possible during bronchial artery embolization to minimize the recurrence of hemoptysis.[17]

Our article highlights the monitoring of body weight as modality to track the progression of CPA (both in terms of radiological and clinical symptoms). This finding may contribute to providing an additional modality for the follow-up of CPA treatment response. ECMM introduced the EQUAL score for monitoring treatment response of CPA. It recommends conducting radiological evaluation, microbiological work-up of respiratory samples through cultures, and serology every 3–6 months or as disease status changes.[3] However, previous studies demonstrated that serological markers such as serum *Aspergillus*-specific IgG and galactomannan showed weak association with therapeutic response.[4,5] In a prospective review, a favourable response, defined as radiological improvement or stable disease, was found to be associated with a significant increase in body weight at the 6th month of treatment (1.6 ± 4.3 kg vs. -2.5 ± 4.5 kg, $p < 0.0001$) compared with those poorly responded.[4] Significant weight gain is defined as an increase of 2 kg at the 4th month and 3 kg at the 6th month post-treatment.[6] Above all, body weight gain can serve as a non-invasive and reliable clinical marker for monitoring treatment response in CPA.

In this patient, we also observed the association between a decreasing trend in HbA1c and symptom stability along with improved chest CT findings. Immunocompromised conditions, such as poorly controlled diabetes mellitus, are known to be associated with CPA.[18] Poorly controlled blood glucose levels can result in dysfunction of T cells, neutrophils, and humoral immunity, prompting susceptibility to various opportunistic infections.[9] Previous studies demonstrated that diabetes is a significant risk factor for both IPA and CPA.[8] For this reason, we maintained HbA1c levels of our patient between 7% and 8%, adhering to the Standards of Care in Diabetes—2023, as published by the American Diabetes Association (ADA). There, they recommend a <7% target level of HbA1c for non-pregnant adults without a history of hypoglycemia, or a less stringent target of HbA1c <8% for patients with multiple comorbidities.[19] In our patient, strict diabetic management and good compliance of antifungal agents are two important factors to reduce the risks of recurrent hemoptysis.

In conclusion, this is the first case report highlights the potential benefits of non-invasive monitoring of CPA activity and the identification of treatment responders through effective blood sugar management and weight gain. Patients with CPA should rigorously control their blood glucose. Optimal blood glucose strategy can complement antifungal therapy in reducing the recurrence of hemoptysis. In addition, monitoring treatment response in CPA through body weight measurements appears to be a useful and practical modality.

AUTHOR CONTRIBUTIONS

T-I. Chuang collected the clinical information and treatment course of patient, and drafted the manuscript. Prof. P-K. Fu drafted the manuscript, revised the manuscript, validated the data, and supervised the study. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, Pin-Kuei Fu, upon reasonable request.

ETHICS STATEMENT

Appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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