

RESEARCH ARTICLE

## Invasive pulmonary aspergillosis: A rare complication after microwave ablation

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### Abstract

Three cases are reported of invasive pulmonary aspergillosis (IPA) occurring after microwave ablation (MWA) for lung tumours. This is a rare complication that has not previously been described in the literature. The diagnosis of IPA was based on the following factors: host factors, clinical manifestations and mycological findings. The first case was a 63-year-old man treated for primary lung squamous carcinoma. Significant tumour regression was achieved by 18 days after MWA, medical treatment with itraconazole for 6 weeks, and postural drainage. The second case, a 65-year-old man, was confirmed with primary lung squamous cell carcinoma. Voriconazole administration using intravenous infusion combined with intracavitary lavage was therapeutically effective after MWA at 1 year follow-up. The third case was a 61-year-old woman with primary lung adenocarcinoma. Delayed pneumothorax and bronchopleural fistula secondary to IPA persisted. The patient died from secondary multiple organ function failure. Despite its very low incidence, the significance of early diagnosis and early administration of antifungal therapy should be highlighted because of the relentless severity of IPA in patients undergoing MWA.

### Introduction

As a minimally invasive interventional technique, image-guided percutaneous microwave ablation (MWA) uses dielectric hysteresis to generate heat, and produces irreversible tumour tissue coagulative necrosis through the transference of hot thermal energy [1]. MWA is widely used in the local treatment of primary and metastatic lung tumours; especially in patients who are poor surgical candidates as a result of severe cardiorespiratory co-morbidity and insufficient vital lung function [2]. Although it is a relatively safe medical modality, MWA in common with radiofrequency ablation (RFA) therapy can lead to some regular complications. These include post-ablation syndrome, pneumothorax, pleural effusion, bleeding, and infection [3,4]. Invasive pulmonary aspergillosis (IPA) infection, as a rare but severe life-threatening complication after percutaneous lung MWA, has not previously been described in the literature. The present study reports on three cases. In each case, IPA after MWA for the treatment of lung tumours was diagnosed based on the following factors: host factors, clinical manifestations, and

### Keywords

Invasive pulmonary aspergillosis, lung neoplasms, microwave ablation

### History

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mycological findings [5]. Written informed consent was obtained for all three patients.

### Case reports

#### Case 1

The first case was a 63-year-old male patient who underwent subtotal gastrectomy for gastric perforation 30 years ago. PET-CT examination in November 2013 showed a single peripheral lesion (40 × 38 mm) in the left lower lobe and a high fludeoxyglucose (FDG) metabolic focus (Figure 1A). Curative surgical resection and radical radiotherapy were precluded after consultations with a thoracic surgeon, pulmonologist and radiologist. MWA was considered as an alternative treatment modality. CT-guided percutaneous lung biopsy of the lesion using a semiautomatic biopsy gun confirmed it as being a poorly differentiated squamous carcinoma. An immediate CT scan following biopsy showed a progressive pneumothorax with consecutive aggravation leading to obvious clinical symptoms. Thereafter a 7F multifunctional drainage tube was placed in the chest cavity. Then the MWA procedure was completed during intermittent manual evacuation of the pneumothorax (Figure 1B). Two weeks after MWA, the patient's symptoms had significantly deteriorated and consisted of a violent cough, large quantities of sticky smoky-grey sputum, dyspnoea, chest congestion and hyperpyrexia ( $\geq 39^\circ\text{C}$ ). The sputum culture yielded colonies

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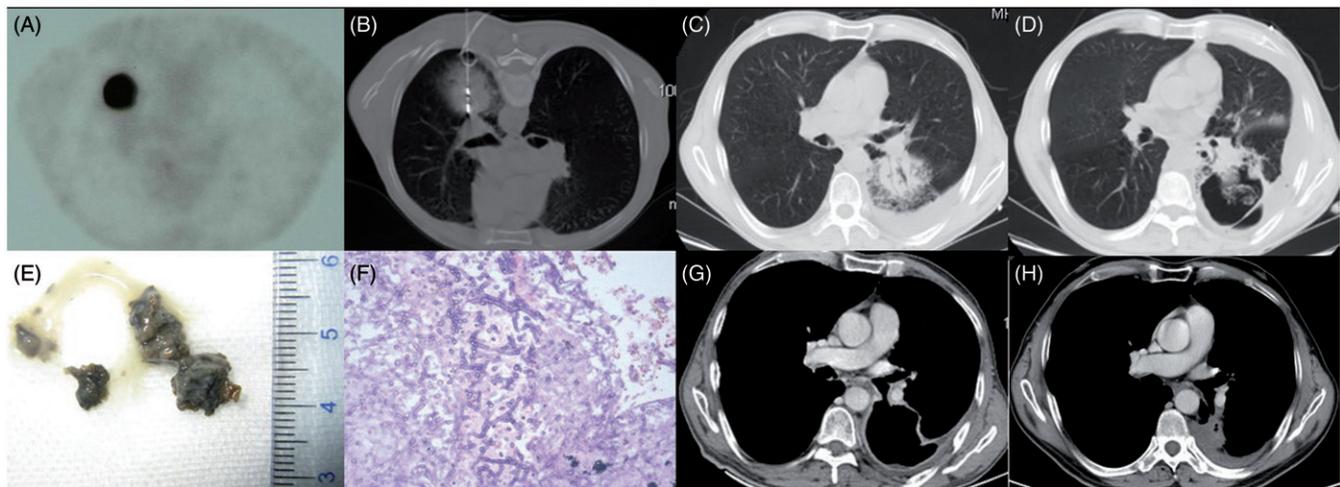


Figure 1. (A) PET-CT image from case 1 showing a single peripheral lesion, 40 × 38 mm, in the superior segment of the left lower lobe and with high FDG uptake before MWA. (B) CT scan showing a drainage tube placed in the pleural cavity and microwave antennas used for MWA. (C) At 10 days after tumour ablation, the ablated area, 55 × 50 mm, displaying GGO and mild pleural effusion. (D) At 18 days after tumour ablation, the ablation zone has been replaced by a large thin-walled cavity containing a mass of irregular consolidation with an air crescent sign. (E) Macroscopic appearance of expectoration. (F) Photomicrograph of expectoration revealing numerous *Aspergillus* hyphae (×40, haematoxylin and eosin staining). (G) A contrast-enhanced CT scan at 7 weeks after MWA showing a thin-walled cavity with a smooth lining and fistula formation between the cavity and left inferior lobar bronchus. (H) An enhanced CT follow-up scan at 6 months after MWA showing gradual involution of the cavity.

of *Aspergillus fumigatus*. The serum levels of  $\beta$ -D-glucan (258.5 pg/mL; normal range,  $\leq 100.5$  pg/mL) and galactomannan (5.22 pg/mL; normal range,  $\leq 0.8$  pg/mL) were abnormally elevated. A sequence of non-contrast-enhanced CT scans revealed the evolution of cavitation from ground glass opacity (GGO) of the lesions (Figure 1C and D). There was also an 'air crescent sign' that appeared as irregular consolidations adhering to the cavity wall after MWA (Figure 1D). After this, initial intravenous and oral voriconazole were administered to the patient at a dose of 200 mg every 12 h for 6 weeks. When the patient was placed in a prone position he could cough up, easily and smoothly, a large volume of phlegm and his symptoms were gradually alleviated. Histopathological examination of the expectoration (Figure 1E) revealed aspergilloma containing numerous *Aspergillus* hyphae (Figure 1F). At about 7 weeks after MWA, an enhanced CT scan (Figure 1G), alleviative symptom presentation, and a lower serological level (galactomannan 1.246) indicated a good efficacy of antifungal drugs and postural drainage. At 6 months after MWA, enhanced follow-up CT showed favourable evolution of the lesion (Figure 1H), manifesting gradual shrinkage of the cavity.

## Case 2

The second patient was a 65-year-old man. In late March 2013, an enhanced CT scan displayed a peripheral neoplasm (36 × 35 mm) in the right upper lobe (Figure 2A). Due to diminished pulmonary function and cardiac/cerebrovascular co-morbidity, the patient had refused any treatment modalities other than image-guided biopsy and MWA. In early April 2013 the patient received a simultaneous percutaneous lung biopsy and MWA (Figure 2B). Histopathological analysis confirmed a highly differentiated squamous cell carcinoma. A real-time chest CT scan during the ablation procedure revealed a limited pneumothorax, which was tolerated and not progressive. Nevertheless, an aggravated pneumothorax was

noted via an immediate chest CT scan after removal of the antennas. A 7F multifunctional tube was placed into the pleural cavity and used for continuous closed drainage for 5 days. At 3 days after the MWA, the patient underwent a non-enhanced follow-up CT scan to check for the presence of a minor pneumothorax and subcutaneous emphysema (Figure 2C). At 3 weeks after MWA, the patient developed a sudden fever of 39.2 °C accompanied by shivering, drastic cough, grey filamentous phlegm and poor efficacy of antibiotic treatment. Dynamic CT scans depicted an atypical imageology involving the evolution of a flake of uneven and faveolate high-density shadow (Figure 2D). Infection by *A. fumigatus* was strongly suspected because of positive results from sputum smear, culturing and assay of serum  $\beta$ -D-glucan and galactomannan. From then on, intravenous voriconazole at a dose of 200 mg was administered every 12 h. At 6 weeks after MWA, the ablation zone presented an uneven thick-walled cavity with an irregular luminal surface, and contained an air–fluid level (Figure 2E). A beaded consolidation was noticed in the cavity with the appearance of an air crescent sign suggestive of aspergilloma (Figure 2E). Percutaneous drainage was performed under CT guidance (Figure 2F) and positive results in sterile conditions from cultures of lavage fluid proved the presence of aspergillosis. The patient was continuously treated with itraconazole for 8 weeks, and attained a favourable therapeutic effect and a high quality of life during a 1-year follow-up period.

## Case 3

The third patient was a 61-year-old woman with a chronic hepatitis B infection for more than 2 years. In April 2013, enhanced whole-body CT and MRI scans revealed a peripheral neoplasm with a diameter of 35 mm adjacent to an oblique fissure in the left lower lobe (Figure 3A). After consultations with a thoracic surgeon and radiologist, the patient refused surgery and radiation therapy and opted for a

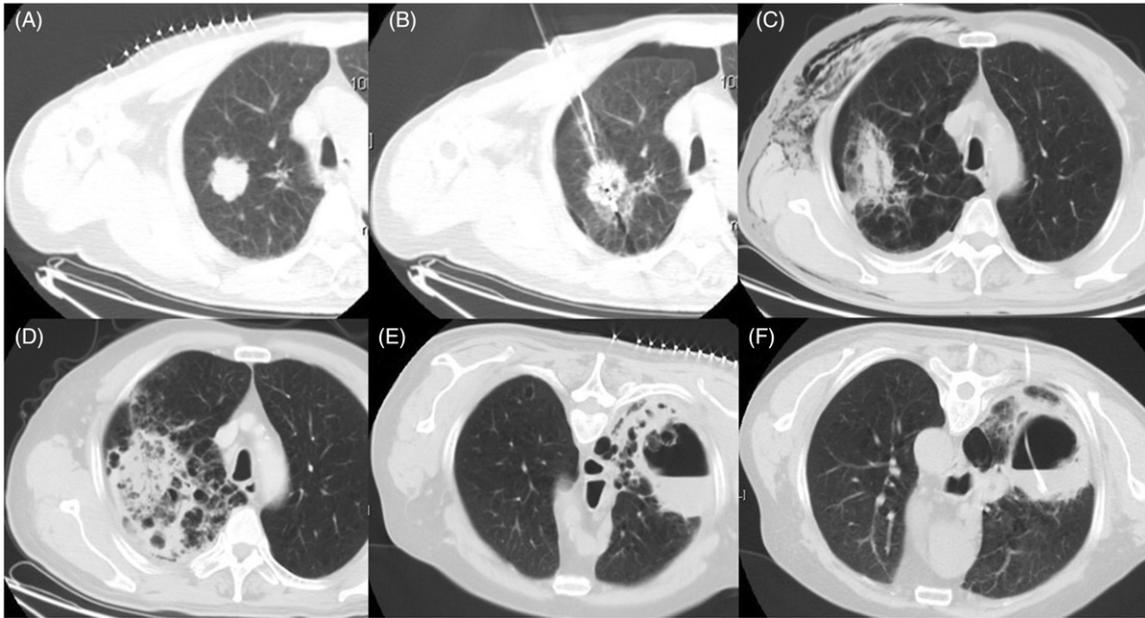


Figure 2. (A) A CT image from case 2 showing an isolated peripheral lesion of  $36 \times 35$  mm located in the anterior segment of the right upper lobe. (B) MWA was performed with a mild pneumothorax. (C) A CT scan showing a minor pneumothorax and ipsilateral subcutaneous emphysema 3 days after MWA. (D) A CT scan depicting a flake of uneven and faveolate high-density shadow 3 weeks after MWA. (E) CT scan at 6 weeks after MWA showing an uneven thick-walled cavity with an irregular luminal surface, containing an air–fluid level and a beaded consolidation. (F) A drainage tube placed into the cavity under CT guidance.

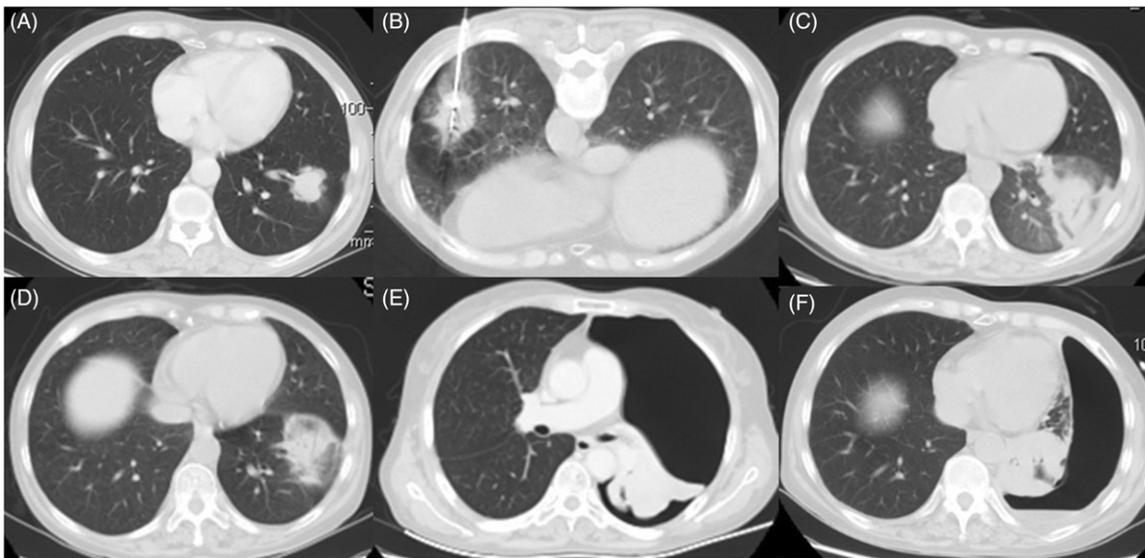


Figure 3. (A) Enhanced CT and MRI scan from case 3 showing a peripheral neoplasm 35 mm in diameter adjacent to an oblique fissure in the left lower lobe. (B) MWA was performed at a power of 70 W for an accumulated total time of 12 min. (C) CT follow-up scan at 48 h after MWA showing a GGO-like reaction band around the lesion encompassing the entire tumour. (D) CT scan on day 10 after MWA showing the stable GGO ablation zone. (E) Enhanced CT scan at 32 days after MWA showing a larger pneumothorax and atelectasis. (F) Follow-up CT scan at 2 months after MWA showing the formation of a bronchopleural fistula within the MWA cavitation that abutted the visceral pleura.

minimally invasive medical modality, namely MWA. The patient underwent a percutaneous lung biopsy and the lesion was histopathologically confirmed as an adenocarcinoma. CT-guided MWA was simultaneously performed without any immediate visible complications (Figure 3B). A CT follow-up scan at 48 h after MWA showed a GGO-like reaction band around the lesion and encompassing the entire tumour (Figure 3C). The GGO in the ablation zone remained stable as depicted by a non-enhanced CT scan on day 10 (Figure 3D). At 15 days after MWA the patient's temperature had risen to

$39.4^{\circ}\text{C}$  with poor efficacy of broad-spectrum antibiotics. A sudden sharp chest pain, leading to feelings of tightness in the chest occurred at 32 days after MWA. This was accompanied by shortness of breath, rapid heart rate, rapid breathing, cough and fatigue, indicating signs of a larger pneumothorax verified by a subsequent enhanced CT scan (Figure 3E). The positive results obtained from serial *Aspergillus* antigen, smear and culturing of the greyish-yellow phlegm revealed an *A. fumigatus* infection. A chest tube was positioned to evacuate the air. Intravenous voriconazole every 12 h was

administered at a dose of 200 mg. Follow-up CT showed the persistence of pneumothorax with no obvious improvement. This signified the formation of a bronchopleural fistula within the MWA cavitation that abutted the visceral pleura (Figure 3F). Because of the uncontrollable IPA, subsequent critical multiple infections and intolerance to surgery, the patient died from secondary multiple organ function failure at 3 months after MWA.

## Discussion

In general, surgical resection provides the best chance of cure for patients with stage I disease [6]. However, insufficient lung function and/or cardiac/cerebrovascular co-morbidity regarding cases 1 and 2 fulfilled the major exclusion criteria ( $FEV1 \leq 50\%$  or diffusing lung capacity for carbon monoxide (DLCO)  $\leq 50\%$ ) for lobectomy (Table 1) [7]. RFA and stereotactic ablative radiotherapy (SABR) can also offer a clear survival benefit in medically inoperable patients with early stage non-small cell lung carcinoma [7,8]. Not wishing to risk pneumonitis, common following SABR (2.1–12.5%) [8], the three patients in our study gave up treatment with SABR. As compared with RFA, MWA used in the lung neoplasma has some advantages, including higher and faster energy convection, a larger ablation zone and a lower heat-sink effect [1,9]. In view of the merits of MWA, three of our patients received percutaneous MWA for the treatment of primary lung cancer (Table 2).

The ubiquitously aerosolising airborne *Aspergillus* conidia, inhaled at least several hundred times daily, is a species of saprophytic thermotolerant fungus that can survive and reproduce on organic debris [10]. A few subtypes of *Aspergillus* such as *A. fumigates*, *A. flavus*, *A. niger* and *A. terreus* can colonise predominantly in the lungs. They can also disseminate to virtually any organ in severely predisposed patients, and cause a spectrum of aspergilloses, classically

defined as invasive, chronic saprophytic and allergic forms [11,12]. *A. fumigatus* is responsible for approximately 90% of human *Aspergillus* infections and is the most frequently recovered aetiological species from cases of invasive aspergillosis [12,13]. In the present study, disease-producing *A. fumigates* were recovered from the three patients.

Based on the level of certainty for the diagnosis of IPA, clinical criteria for proven (definitive), probable, and possible infection mainly consist of three elements: host factors; clinical manifestations; and mycological findings [5,13]. The relevant literature reports the risk of developing IPA among patients with positive culture results for *Aspergillus* species as 9% for those with underlying pulmonary diseases, 8% for those with solid-organ cancer, and 27% for those with malnutrition [13], which were categorised as of intermediate risk for IPA. Based on the criteria for defining cases of IPA [5,12,13], cases 1 and 2 were classified as proven (definitive) IPA, and case 3 as probable IPA (Table 3).

*Aspergillus* infection occurring after tumour ablation has only been reported in two previous studies. Hiraki et al. reported a case of pulmonary aspergilloma infection in a cavity formed after RFA [14], and Alberti et al. reported two cases of pulmonary aspergilloma secondary to cavitation after RFA [15]. The common features of the three cases above are summarised as follows.

- (1) They underwent percutaneous RFA procedures rather than MWA, from one to three times on account of recurrent or metastatic lesions.
- (2) Pulmonary aspergilloma was confirmed in all three cases by means of histological examination of the surgical or biopsy specimen. It was defined as a chronic saprophytic form of aspergillosis distinct from IPA [5,12].
- (3) The *Aspergillus* infections in the three cases were all secondary to cavitation and occurred at 4–8 months after tumour ablation.

Table 1. Patient characteristics.

Case no.	Gender	Age (years)	Co-morbidity	Lung function (FEV1, DLCO)	Smoking index	Site of tumour	Tumour size (mm)	Lymph node metastases	Distant metastasis	Stage
1	Male	63	COPD (emphysema)	39.1%, 13.1%	1350	Left lower lobe	40	no	no	Ib
2	Male	65	COPD (emphysema), cardiac/cerebrovascular disease	44.2%, 66.7%	1200	Right upper lobe	36	no	no	Ib
3	Female	61	CHB (active phase), mild malnutrition	122.2%, 59.4%	None	Left lower lobe	35	no	no	Ib

Table 2. Ablation, microbiology and treatment characteristics for the three cases.

Case no.	Number of antennas	Number of ablation sites	Total time of ablation (min)	Power of ablation (W)	<i>Aspergillus</i> species	Co-infection	Antifungal drug	Adjuvant therapy	Outcome
1	2	4	15	70	<i>Aspergillus fumigates</i>	<i>Acinetobacter baumannii</i> , <i>Staphylococcus aureus</i>	Voriconazole	Postural drainage Intracavitary lavage	Cure, alive
2	2	2	14	70	<i>Aspergillus fumigates</i>	None	Voriconazole	Intracavitary lavage	Cure, alive
3	2	3	12	70	<i>Aspergillus fumigates</i>	<i>Klebsiella pneumoniae</i>	Voriconazole	Closed drainage of pleural cavity	Death

Table 3. Level of certainty for the diagnosis of IPA for the three cases.

Case no.	Host factors	Clinical manifestations (imageology)	Mycological positive findings ( <i>Aspergillus fumigatus</i> )	Serological $\beta$ -D-glucan, galactomannan	Certainty of IPA
1	Primary lung cancer, COPD (emphysema)	Thin-walled cavity within an area of irregular consolidation (an air crescent sign)	Histopathological examination of the expectoration	Positive	Definitive
2	Primary lung cancer, COPD (emphysema)	Uneven thick-walled cavity within an area of beaded consolidations	Cavity lavage fluid cultures in sterile conditions	Positive	Definitive
3	Primary lung cancer, chronic hepatitis B, malnutrition	Delayed pneumothorax, a broncho-pleural fistula, pleural effusion and atelectasis	More than twice from sputum smears and cultures	Positive	Probable

(4) An air crescent sign, which occurred in two cases, is a typical radiological sign of pulmonary aspergilloma, but the appearance of the CT image in the third case was atypical, assuming a thickening of the cavity.

Incidence of IPA after MWA has not previously been reported. In our experience of 591 procedures, a total of three cases conformed to the diagnostic criteria, an incidence of 0.5%. These three cases had the following common characteristics.

- (1) *Aspergillus* infections took place before cavity formation. Perhaps the organic tissue in the coagulative necrosis after MWA provided a good medium for colonisation, growth, and reproduction of inhaled *Aspergillus* conidia.
- (2) Sudden high fever, fatigue and obvious symptoms of lower respiratory tract occurred in every case following short-term stability.
- (3) IPA in the three cases tended to occur 2–4 weeks after MWA accompanied by grey filamentous phlegm.
- (4) Laboratory tests revealed highly positive  $\beta$ -D-glucan and galactomannan.
- (5) IPA that occurred after MWA was likely to result in secondary bacterial infection (Cases 1 and 3; Table 2).

In addition, all the three cases in our present study underwent MWA with the application of double antennas at 2–4 sites for the purpose of cure, which may have enlarged the necrotic scope of ablation and facilitated the occurrence of aspergillosis. The substantial progress in thermal modelling and temperature distribution of MWA to provide 3D temperature information [16,17] may be useful for predicting the temperature field and appropriate ablation area to reduce the incidence of fungal infection and other complications.

IPA will usually progress to relentless lethal pneumonia without adequate therapy, which can further disseminate to the central nervous system or extend to contiguous intrathoracic structures [12]. A progressive necrotising pneumonia caused by IPA in case 3 resulted in intractable delayed pneumothorax, bronchopleural fistula and co-infection, and was the cause of death. It is recommended that in most patients with strongly suspected invasive aspergillosis there is early initiation of antifungal therapy using intravenous or oral voriconazole as the primary treatment. This should be continued for a minimum of 6–12 weeks [12]. Voriconazole at a dose of 200 mg every 12 h was administered to cases 1 and 2 for 6 weeks and 8 weeks, respectively (Table 2), in combination with postural drainage (case 1) and intracavitary lavage (case 2). Follow-up of case 1 at 6 months and case 2 at 1 year indicated recovery from IPA after MWA.

Our three cases were confirmed with IPA secondary to MWA, which is a rare but life-threatening complication. Hospitalisations for the three cases cost substantially more than for other cases. Stays in hospital were lengthy and one of the cases died.

### Declaration of interest

Guanghui Huang and Qi Liu contributed equally to the article. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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