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**Case Report / Приказ болесника**

Irena Đunić<sup>1,2,\*</sup>, Maja Ercegovač<sup>2,3</sup>, Milena Todorović Balint<sup>1,2</sup>

**Combined treatment of pulmonary mucormycosis with isavuconazole and thoracic surgery in a patient with acute myeloid leukemia**

Комбиновано лечење плућне мукормикозе исавуконазолом и торакалном хирургијом код болесника са акутном мијелоидном леукемијом

<sup>1</sup>University Clinical Center of Serbia, Clinic for Hematology, Belgrade, Serbia;

<sup>2</sup>University of Belgrade, Faculty of Medicine, Belgrade, Serbia;

<sup>3</sup>University Clinical Center of Serbia, Clinic for Thoracic Surgery, Belgrade, Serbia

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**\*Correspondence to:**

Irena ĐUNIĆ

Clinic for Hematology, University Clinical Center of Serbia, 2 Koste Todorovića Street, Belgrade 11000, Serbia

e-mail: [irenadjunic04@gmail.com](mailto:irenadjunic04@gmail.com)

## Combined treatment of pulmonary mucormycosis with isavuconazole and thoracic surgery in a patient with acute myeloid leukemia

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### SUMMARY

**Introduction** Invasive pulmonary mucormycosis is one of the most severe and potentially fatal fungal infections in immunocompromised patients, particularly in recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT). Diagnosis and treatment of pulmonary mucormycosis remain challenging.

**Case outline** We present a 19-year-old male patient with relapsed acute myeloid leukemia (AML) following allo-HSCT whose treatment was complicated by proven pulmonary mucormycosis. The infection was managed using an integrated medical and surgical approach, including liposomal amphotericin B with dose escalation, prolonged treatment with oral isavuconazole, and right lower lobectomy. Postoperatively, the patient developed *Pseudomonas aeruginosa* sepsis and pneumothorax requiring drainage; both complications were successfully managed. Subsequent computed tomography (CT) scans demonstrated regression and complete radiological resolution of the pulmonary lesion.

**Conclusion** This case illustrates the complexity of managing pulmonary mucormycosis in a severely immunocompromised patient with relapsed AML after allo-HSCT and concomitant graft-versus-host disease (GVHD). Successful management required a multidisciplinary approach combining antifungal therapy and thoracic surgery, followed by prolonged antifungal treatment and close radiological monitoring.

**Keywords:** allo-HSCT; AML relapse; pulmonary mucormycosis; isavuconazole; liposomal amphotericin B; thoracic surgery

### САЖЕТАК

**Увод** Инвазивна плућна мукормикоза представља једну од најтежих и потенцијално фаталних гљивичних инфекција код имунокомпромитованих болесника, посебно код болесника након алогене трансплантације матичних ћелија хематопоезе (*allo-HSCT*). Дијагностика и лечење плућне мукормикозе представљају значајан клинички изазов.

**Приказ болесника** Приказујемо 19-годишњег болесника са релапсом акутне мијелоидне леукемије (AML) након *allo-HSCT*, код кога је лечење било компликовано доказаном плућном мукормикозом. Инфекција је лечена комбинованим медицинско-хируршким приступом, који је укључивао липозомални амфотерицин Б уз ескалацију дозе, дуготрајну примену исавуконазола и доњу десну лобектомију. У постоперативном периоду болесник је развио сепсу изазвану бактеријом *Pseudomonas aeruginosa* и пнеумоторакс који је захтевао дренажу; обе компликације су успешно збринуте. На контролним СТ прегледима регистрована је регресија, а потом и комплетна радиолошка резолуција плућне лезије.

**Закључак** Овај приказ указује на сложеност лечења плућне мукормикозе код тешко имунокомпромитованог болесника са релапсом AML након *allo-HSCT* и истовременом GVHD. Успешно лечење захтевало је мултидисциплинарни приступ који је укључивао антифунгалну терапију и торакалну хирургију, након чега је настављена продужена антифунгална терапија уз пажљиво радиолошко праћење.

**Кључне речи:** *allo-HSCT*; релапс AML; плућна мукормикоза; исавуконазол; липозомални амфотерицин Б; торакална хирургија

### INTRODUCTION

Mucormycosis is an opportunistic invasive fungal infection caused by fungi of the order Mucorales. A characteristic feature of these fungi is their propensity for angioinvasion, leading to vascular thrombosis, tissue ischemia, and necrosis. Mucormycosis is a rapidly progressive infection associated with substantial morbidity and mortality, particularly in severely immunocompromised patients [1–3].

Major risk factors include prolonged and profound neutropenia, corticosteroid exposure, hematopoietic stem cell or solid-organ transplantation, poorly controlled diabetes mellitus, and other conditions associated with impaired host immunity [4–6]. Depending on the site of infection, mucormycosis may present as rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, or other less

common forms [1]. Although mucormycosis remains relatively uncommon, an increasing incidence has been reported in several patient populations and geographic regions [1, 7].

In immunocompromised patients, particularly recipients of allo-HSCT, pulmonary mucormycosis is associated with a high risk of mortality. Mucorales spores can interact with host endothelial and epithelial cells, facilitating tissue invasion and angioinvasion. In healthy individuals, fungal spores and hyphae are eliminated primarily through the activity of phagocytic cells and neutrophils. Impaired phagocytic function and prolonged neutropenia therefore substantially increase susceptibility to invasive disease [4, 8–10].

Diagnosis and treatment of pulmonary mucormycosis in allo-HSCT recipients remain challenging. Histopathological examination of affected tissue is an important component of diagnosis, particularly when fungal elements are demonstrated within tissue [11]. Clinical and radiological findings are often nonspecific, and definitive diagnosis may require bronchoscopy and tissue sampling.

Historically, treatment options for mucormycosis were limited, with amphotericin B formulations representing the mainstay of therapy. Mucorales are intrinsically resistant to several antifungal agents commonly used for other invasive fungal infections, including voriconazole and the echinocandins [4, 10]. Treatment outcomes depend on the patient's underlying condition, immune status, extent and site of disease, and the possibility of achieving adequate surgical source control.

Isavuconazole is a broad-spectrum triazole antifungal agent available in both oral and intravenous formulations. It is administered as the water-soluble prodrug isavuconazonium sulfate, which is rapidly converted to isavuconazole in plasma. Isavuconazole inhibits fungal cytochrome P450-dependent ergosterol biosynthesis and has predictable pharmacokinetics and a prolonged half-life, allowing once-daily maintenance dosing. Importantly, the intravenous formulation does not contain the cyclodextrin vehicle used with intravenous voriconazole, which may be advantageous in patients with renal impairment [7, 8].

Here, we present a case of pulmonary mucormycosis in a patient with relapsed AML after allo-HSCT and concomitant GVHD who was successfully managed with liposomal amphotericin B, prolonged isavuconazole therapy, and thoracic surgery.

## CASE REPORT

We present a 19-year-old male patient with AML whose treatment was complicated by pulmonary mucormycosis and required both medical and surgical treatment.

The diagnosis of AML with a complex karyotype was established in December 2022, and the patient was treated according to the Berlin-Frankfurt-Münster 2004 protocol. Following completion of chemotherapy, he underwent matched unrelated donor (MUD) allo-HSCT in June 2023.

Post-transplant relapse occurred in August 2024, and salvage treatment with FLA-IDA was administered, resulting in complete morphological remission. A chest computed tomography (CT) scan

performed in September 2023 revealed a small right paracardial consolidation (Figures 1 and 2). The patient had been receiving primary antifungal prophylaxis with oral posaconazole suspension at a dose of 5 mL three times daily.

Assessment of minimal residual disease (MRD) demonstrated 0.08% leukemic cells in the bone marrow. Treatment was subsequently continued with venetoclax and azacitidine (Ven-Aza). On day 8 of the second cycle, donor lymphocyte infusion (DLI) was administered.

In November 2024, during the second cycle of Ven-Aza, the patient developed prolonged febrile neutropenia accompanied by respiratory symptoms. Serial chest CT scans demonstrated progression of necrotizing pneumonia despite broad-spectrum antimicrobial therapy. Venetoclax was therefore discontinued in November 2024 (Figures 3–5).

Bronchoscopy was performed, and histopathological examination confirmed pulmonary mucormycosis. Liposomal amphotericin B was initiated at 5 mg/kg/day and subsequently increased to 7 mg/kg/day because of radiological progression.

Follow-up CT performed in February 2025 demonstrated further progression of the pulmonary lesion, prompting a multidisciplinary treatment approach. Surgical treatment was recommended by the thoracic surgery team but was temporarily delayed because the patient developed grade III acute GVHD involving the liver and intestines. GVHD was treated with corticosteroids, ruxolitinib, and extracorporeal photopheresis (ECP).

The patient's clinical course was further complicated by cytomegalovirus (CMV) reactivation, which was treated with maribavir for five weeks. Following control of CMV reactivation and partial stabilization of GVHD, a right lower lobectomy was successfully performed in March 2025.

In the postoperative period, the patient developed *Pseudomonas aeruginosa* sepsis, which was treated with antibiotics according to the susceptibility profile, as well as pneumothorax requiring drainage (Figure 6). Both complications were successfully managed.

In April 2025, long-term antifungal therapy with oral isavuconazole was initiated as salvage treatment at a loading dose of 200 mg three times daily for two days, followed by 200 mg once daily. The treatment was initially continued for four months.

A follow-up CT scan in July 2025 revealed a new pulmonary lesion suspicious for recurrent mucormycosis. Because the patient remained immunosuppressed due to mild chronic hepatic GVHD, isavuconazole therapy was extended for an additional nine months.

Subsequent CT scans performed in October 2025 and April 2026 demonstrated progressive regression and ultimately complete resolution of the pulmonary lesion (Figure 7). GVHD subsequently resolved, and treatment with ruxolitinib was discontinued.

Azacitidine treatment was continued because MRD remained positive at the last assessment in May 2026, with 0.09% leukemic cells detected in the bone marrow.

## DISCUSSION

Mucormycosis is an invasive fungal infection caused by fungi of the order Mucorales and predominantly affects patients with impaired immune defenses [1]. Hematological malignancies, prolonged neutropenia, corticosteroid exposure, and hematopoietic stem cell transplantation are among the most important risk factors for invasive mold infections [4, 12–15]. Pulmonary involvement is particularly important in patients with hematological malignancies and allo-HSCT because of its association with substantial mortality.

The clinical manifestations of pulmonary mucormycosis are nonspecific and may include fever, cough, dyspnea, chest pain, and hemoptysis. In a case series by Bao et al. involving 21 patients with pulmonary mucormycosis following allo-HSCT, the mean age was 43 years and 90.5% of patients were male. AML was the most common underlying hematological malignancy, accounting for 57.1% of cases, while 38.1% of patients had previously developed GVHD. Treatment included single-agent amphotericin B in 33.3% of patients, combination antifungal therapy including amphotericin B in 42.9%, and combined medical and surgical treatment in 9.5%. The reported one-year mortality rate was 71.4% [1].

Our patient was considerably younger, at 19 years of age, but had several major risk factors for invasive fungal infection. These included relapsed AML following allo-HSCT, prolonged and profound immunosuppression, GVHD requiring immunosuppressive therapy, and prolonged neutropenia. Despite antifungal prophylaxis with posaconazole, pulmonary mucormycosis developed and subsequently progressed during treatment.

An important component of management in this case was escalation of liposomal amphotericin B from 5 to 7 mg/kg/day in response to radiological progression. However, medical therapy alone was insufficient to achieve disease control. Surgical resection was therefore pursued once the patient's clinical condition and GVHD allowed thoracic surgery to be performed. The combination of antifungal treatment and surgical resection was followed by complete radiological resolution.

Lei et al. [4] recently reported a systematic review and meta-analysis of mucormycosis in pediatric patients following hematopoietic stem cell transplantation. Among 32 individual patients included in the analysis, AML was reported in 25%, and 75% of these patients had relapsed disease. Prior antifungal prophylaxis had been administered in 63% of patients. Pulmonary involvement accounted for 28% of cases, while overall mortality was 44%. Intravenous amphotericin B was the predominant initial treatment, while maintenance therapy most frequently included oral posaconazole, followed by lower-dose liposomal amphotericin B and itraconazole. The median duration of maintenance therapy was 185 days (range, 114–270 days).

The same review also suggested a potential benefit of surgical intervention when feasible. However, the available evidence is based predominantly on small retrospective series and case reports, and treatment decisions must therefore be individualized according to the extent of disease, anatomical localization, underlying malignancy, immune status, and surgical fitness.

Our patient received prolonged oral isavuconazole as salvage treatment following surgical resection. After four months of therapy, a new pulmonary lesion suspicious for recurrent mucormycosis was identified on CT. Because of persistent immunosuppression associated with chronic hepatic GVHD, isavuconazole therapy was extended for an additional nine months. Subsequent CT examinations demonstrated progressive regression and ultimately complete radiological resolution of the lesion.

Isavuconazole may represent a useful therapeutic option in selected patients with mucormycosis, particularly when prolonged antifungal therapy is required. Its oral formulation, once-daily maintenance dosing, predictable pharmacokinetics, and absence of cyclodextrin in the intravenous formulation may offer practical advantages in complex immunocompromised patients [7, 8]. Nevertheless, the evidence supporting its use in mucormycosis remains substantially less extensive than that for liposomal amphotericin B, and treatment should be individualized.

Peixoto et al. [15] reported a case of disseminated mucormycosis involving the lung, brain, and skin in a patient with relapsed AML following allo-HSCT. After failure of posaconazole and intolerance to amphotericin B, the patient was successfully treated with isavuconazole for more than six months. This case, together with our experience, supports the potential role of prolonged isavuconazole therapy as part of an individualized treatment strategy in complex patients with mucormycosis.

Our case illustrates the complexity of managing pulmonary mucormycosis in a severely immunocompromised patient with relapsed AML after allo-HSCT and concomitant GVHD. Successful management required a multidisciplinary approach combining antifungal therapy and thoracic surgery. Treatment included liposomal amphotericin B with dose escalation, prolonged treatment with isavuconazole, and surgical resection. Despite severe postoperative complications, including *Pseudomonas aeruginosa* sepsis and pneumothorax, the patient ultimately achieved complete radiological resolution of pulmonary mucormycosis.

**Ethics:** Written informed consent was obtained from the patient for publication of this case report and any accompanying images. All identifying details have been removed to ensure patient privacy.

**Conflict of interest:** None declared.

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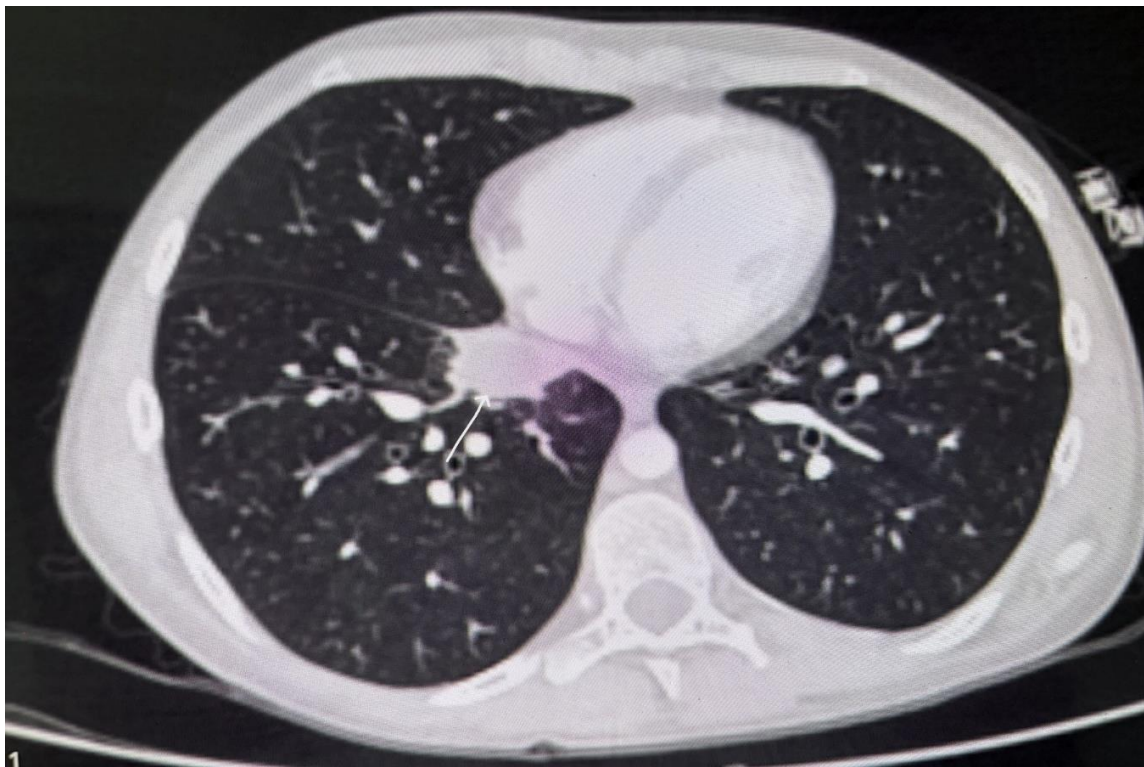


**Figure 1.** Computed tomography scan of the lung window of the right paracardial incipient pulmonary consolidation



**Figure 2.** Computed tomography scan of the soft tissue window of the right paracardial incipient pulmonary consolidation



**Figure 3.** Computed tomography scan of the lung window of necrotizing pneumonia progression – pulmonary mucormycosis

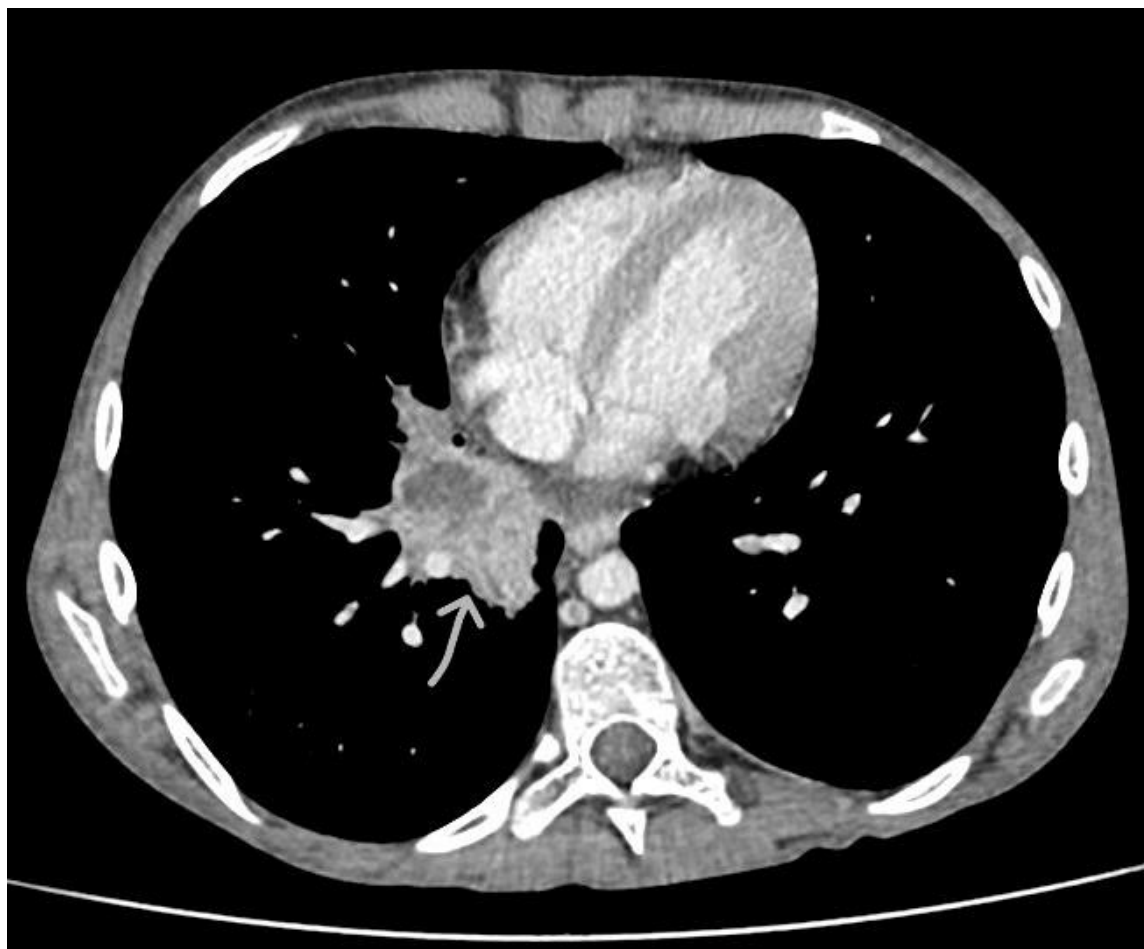


**Figure 4.** Computed tomography scan of the soft tissue window of necrotizing pneumonia progression – pulmonary mucormycosis

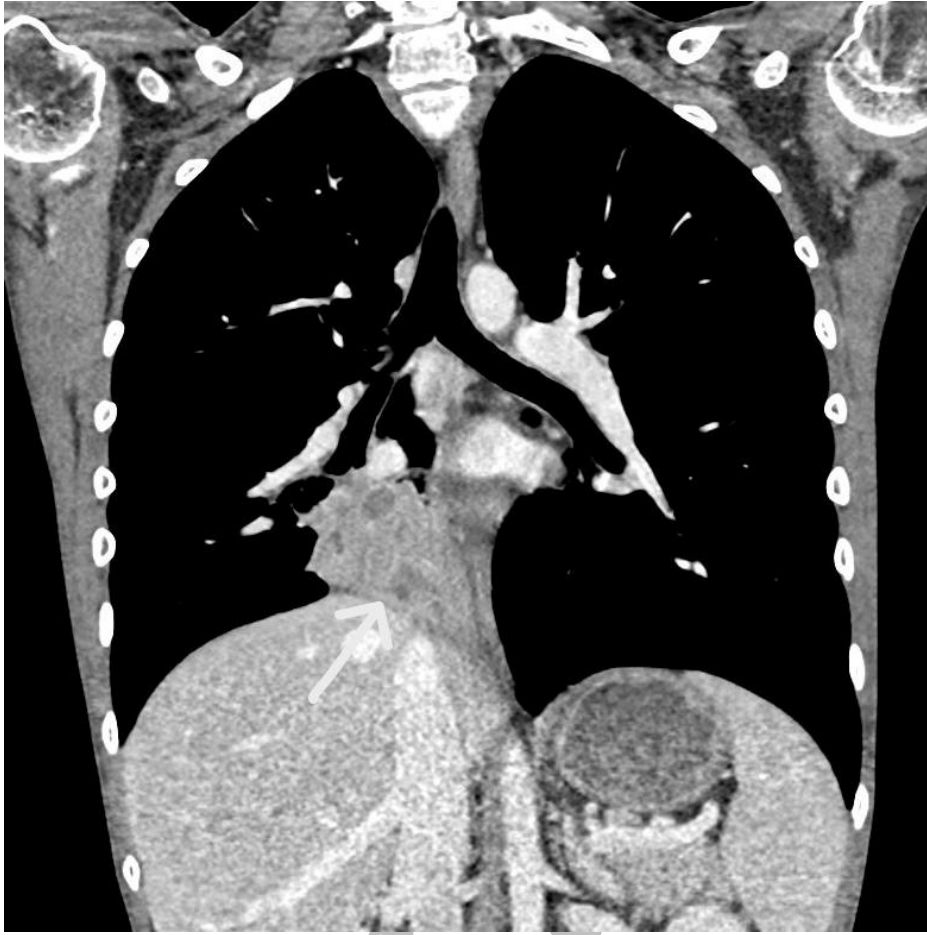


**Figure 5.** Coronary computed tomography scan of the progression of pulmonary mucormycosis

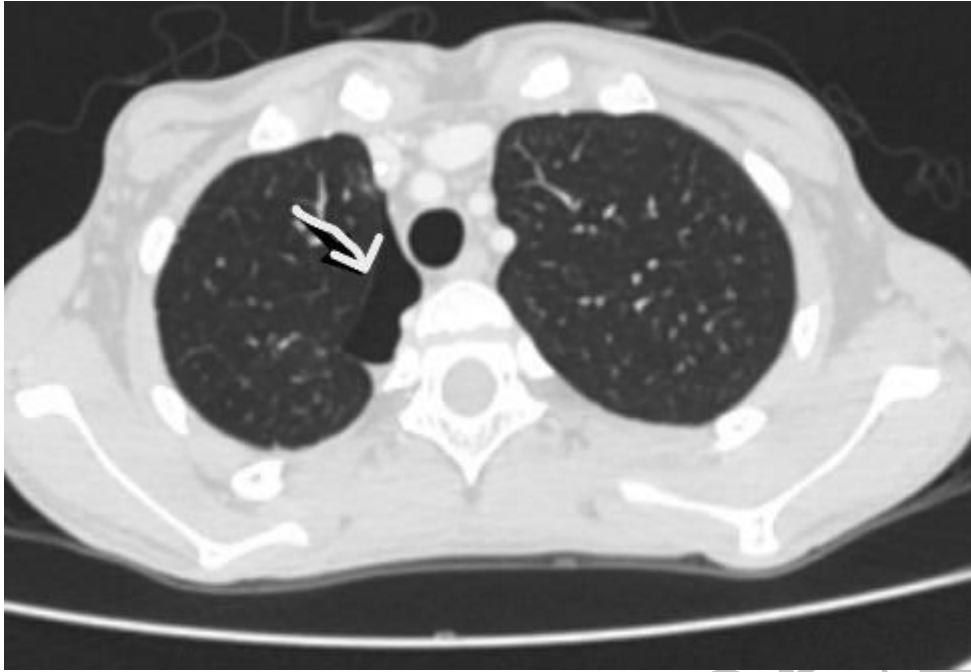


**Figure 6.** Postoperative pneumothorax



**Figure 7.** Postoperative sequelae