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Successful management of gastropulmonary fistula due to invasive fungal infection after chemotherapy and autologous stem cell transplantation: a case report

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Background. Invasive fungal infections (IFI) contribute significantly to mortality and morbidity in patients receiving myelosuppressive chemotherapy for hematologic malignancies. Acquired gastropulmonary fistula is a rare complication of IFI.

Material and methods. We present a case history of a patient with malignant myeloma. She was treated with autologous stem cell transplantation and chemotherapy for three years. She had been treated with antifungal agents as well. Following a specific treatment, she developed an invasive fungal infection (IFI) of the left lung which had been complicated with left gastropulmonary fistula. The patient's general condition was deteriorating, so it was decided to perform a surgical intervention. At the first procedure, open-window thoracostomy was created in order to facilitate treatment by daily packing of the cavity. Four weeks after the thoracostomy, a thoracomyoplasty was performed to repair a gastropleural fistula. During the laparotomy, the gastric fundus was freed from adjacent tissues and repaired. Intrathoracic transposition of the latissimus dorsi and anterior serratus muscle flaps was performed simultaneously to create a new diaphragm. The open-window thoracostomy was left open due to some small bronchial fistulas. The thoracostomy opening healed spontaneously during the following six months.

Conclusion. We report what is, to the best of our knowledge, the first case of an invasive fungal infection (*Geotrichum capitatum*) successfully treated with intravenous amphotericin B, voriconazole, and surgery on infected soft tissues (organs) for a patient with multiple myeloma in prolonged neutropenia. The efficacy and safety of the surgery for infected soft tissues requires further evaluation.

Keywords: invasive fungal infection after immunosuppresive chemotherapy, pulmonary resection, acquired gastropulmonary fistula

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INTRODUCTION

Treatment of multiple myeloma generally consists of chemo-immunotherapy and autologous stem cell transplantation, with the latter prolonging disease-free survival and overall survival. Nowadays, myeloma is a chronic condition, the relapses and salvage therapies of the disease result in cumulative immunosuppression and a higher risk of infection (8). Infection is a significant cause of morbidity and mortality in patients with multiple myeloma (7, 8).

In recent years, the most important advances in the treatment of transplant recipients and patients with haematological neoplasm have been accompanied by an increase in the incidence of the common fungal diseases and the emergence of some less common ones. Although new techniques (e. g., galactomannan detection) and new antifungals have appeared, these opportunistic infections remain difficult to diagnose and lead to a high mortality.

Some types of fungi can cause rare infections. One of them is *Saprochaete capitata* (formerly known as *Geotrichum capitatum* and *Blastoschizomyces capitatus*). It is a non-fermentative, non-encapsulated, urease-negative ascomycetous yeast (2, 3). It is a ubiquitous fungus (2). *S. capitata* is part of the normal microbiota of the human skin and is frequently isolated from sputum and the digestive tract of healthy people (1). Invasive human infection is rare.

Mostly, amphotericin and flucytosine are used for antifungal treatment, but experience is limited (3–6). Less data is available on voriconazole, but in vitro susceptibility is promising (3, 4).

We encountered a complete gastropulmonary fistula resulting from an invasive fungal infection in a patient with myeloma. The patient was successfully cured after a couple of surgical interventions.

CASE HISTORY

A 46-year-old woman presented with a persistent dry cough and vague left pleuritic pain that had worsened over the preceding three weeks.

The patient had a history of multiple myeloma (MM) since 2011. In June 2011, when she was 41 years old, asymptomatic multiple myeloma (immunoglobulin (Ig) A lambda) was diagnosed. Her bone marrow showed 70% plasma cells with Ig lambda light chain restriction, IgA-26 g/l.

The patient's first-line therapy consisted of a weekly regimen of oral CTD (cyclophosphamide 300 mg/m^2 weekly, dexamethasone 40 mg, and thalidomide 100 mg). After four cycles, she achieved a very good partial response. Then, at 24 November 2011, she underwent autologous stem cell transplantation with minimal complications. The patient remained in remission for two years after the transplantation and then relapsed in September 2013.

The patient's second-line therapy consisted of a weekly regimen of oral cyclophosphamide (300 mg/m^2), subcutaneous bortezomib (1.3 mg/m^2), and oral dexamethasone 40 mg (CyBorD; also known as VCD). After four cycles, the patient achieved a very good second partial remission. The second autologous HSCT was performed on 9 January 2014 for consolidation. The patient remained in remission for 9 months after the transplantation and then relapsed MM in November 2014. Her blood data showed increased Ig A (g/L) – 48.44, B2 microglobulin (mg/L) – 8.82, total protein (g/l) – 113.9, M gradient (%) – 39.8, anaemia HGB (g/l) – 84. The third-line therapy – VTD-PACE regimen (bortezomib, thalidomide, dexamethasone, platinum, adriamycin, cyclophosphamide, and etoposide). After three cycles, the patient achieved a very good third partial remission. Then, the third autologous HSCT was performed.

Due to relapses, she received three lines of chemotherapy during four years of disease, each time receiving induction chemotherapy and high-dose chemotherapy with autologous peripheral blood stem cell transplantation (ASCT) for consolidation. After the last ASCT, which was performed on 11 March 2015, the patient had prolonged neutropenia and neutropenic fever.

On admission, her chest radiograph revealed subtle patchy consolidation in the left lower lobe and collection of fluid in the left pleural cavity (Fig. 1). She was treated with antibiotics (meronem and linesolid). Due to a probable fungal infection of the lungs, antifungal agents were administered (amphotericin B (1 mg/kg/24 hours), micafungin (300 mg/24 hours), voriconazole (600 mg/24 hours)). However, her general condition deteriorated and localized left pyopneumothorax was diagnosed (Figs. 2, 3). Further work-up included fiberoptic gastroscopy and a computed tomography scan of the chest (Fig. 4). The CT showed a partial necrosis of the gastric fundus and left

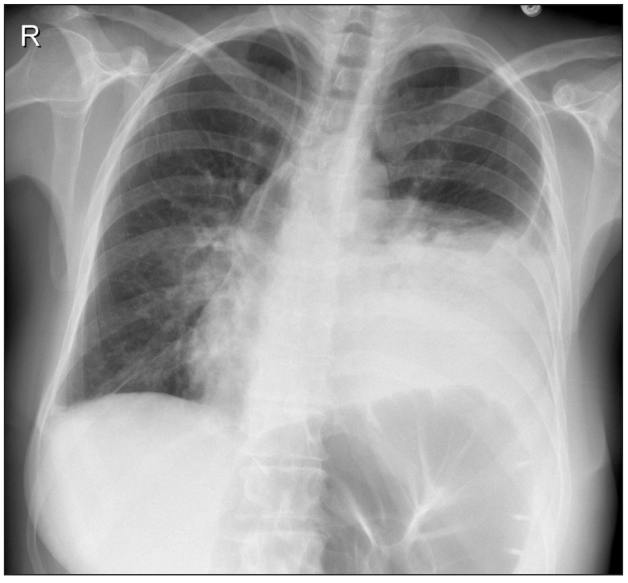

Fig. 1. Chest radiograph with a collection of fluid in the left pleural cavity (9 April 2015). A marked infiltration of the basal segments of the left lower lobe is presented

diaphragm, and clear communication of the stomach lumen with left pleural cavity. Fiberoptic gastroscopy was performed at the operation theatre right before the incision. It revealed a localised necrotic area of the fundus of the stomach. The area was covered with necrotic debris which was moving

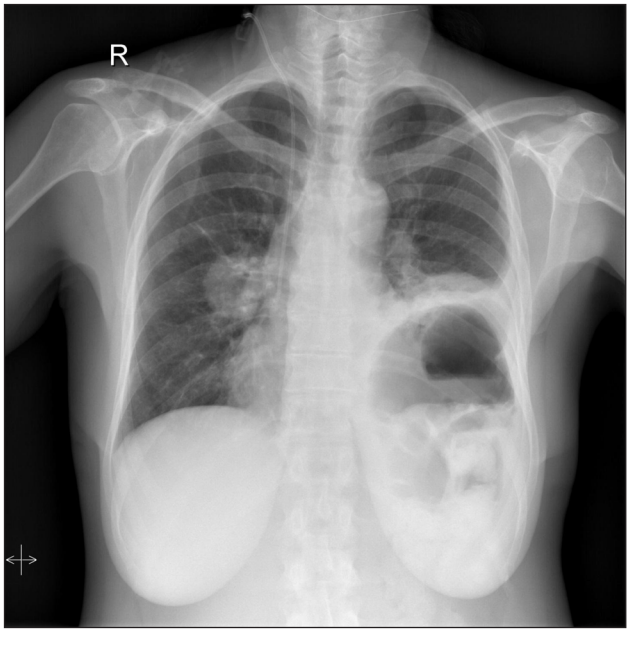

Fig. 2. Chest radiograph following one month after the initial investigation. Two air-fluid levels are clearly visible in the left side

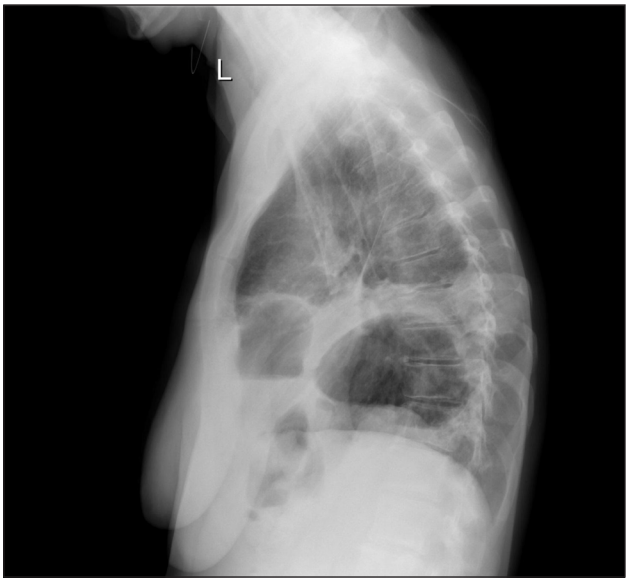

Fig. 3. A lateral view

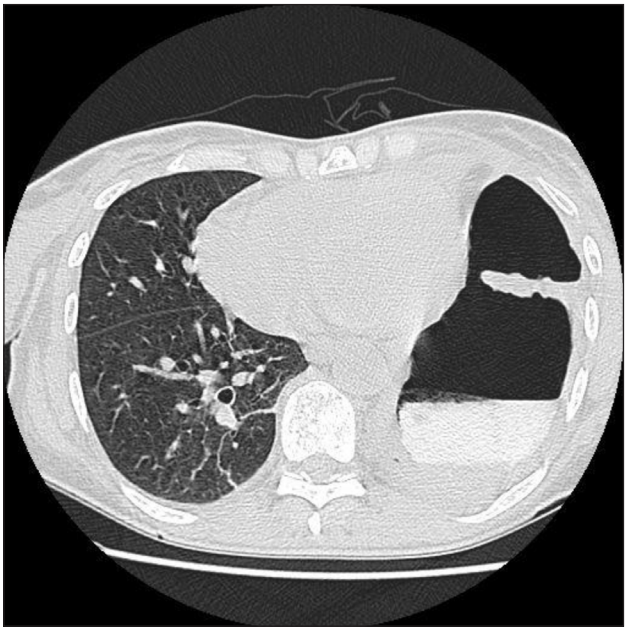

Fig. 4. Same-day CT scan of the chest. The contrast medium is clearly visible in the stomach. A short communication of the stomach lumen with the left pleural cavity through the diaphragmic defect was evaluated

in conjunction with artificial ventilation. It was decided that the patient had a severe left-sided pleural empyema of fungal origin with bronchopleural and gastropleural fistulas at once. The Eloesser open-flap procedure with resection of VII–VIIIth subjacent posterolateral ribs was performed. Upon exploration, part of the lower lobe was found partially necrotized and was atypically resected using

staplers. A huge ventriculopleural communication (about 5 cm in diameter) and a defect in the diaphragm were evaluated (Fig. 5). An open-window thoracostomy was created in order to facilitate treatment by daily packing of the cavity (Fig. 6). During open-window thoracostomy, the latissimus dorsi muscle was preserved with minimal injury to the anterior serratus muscle.

The invasive fungal disease of *Geotrichum capitatum* was confirmed from the operative specimen culture that was found to be resistant to fluconazole (MIC 48 μg/ml). Other antifungal agents as voriconazole (MIC 0.75 μg/ml), Amphotericin B (MIC 0.38 μg/ml), Anidulafungin (MIC 12 μg/ml), were reported with no interpretation. The susceptibility was assessed by the E-test procedure.

Both amphotericin and voriconazole were used for antifungal treatment. Following surgery, the patient also received prolonged antifungal treatment with voriconazole.

Four weeks after the thoracostomy, thoracomyoplasty was performed to repair the gastropleural fistula. On laparotomy, the gastric fundus was freed from adjacent tissues and repaired. Intrathoracic transposition of the latissimus dorsi and anterior serratus muscle flaps was performed simultaneously to create a new diaphragm. The open-window thoracostomy was left open due to some small bronchial fistulas. The thoracostomy opening healed spontaneously during the following six months (Fig. 7, 8).

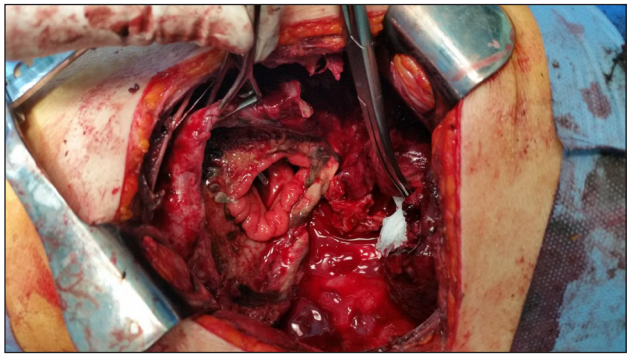

Fig. 5. An intraoperative view. A large defect of the stomach fundus is clearly visible in the centre of the operative field

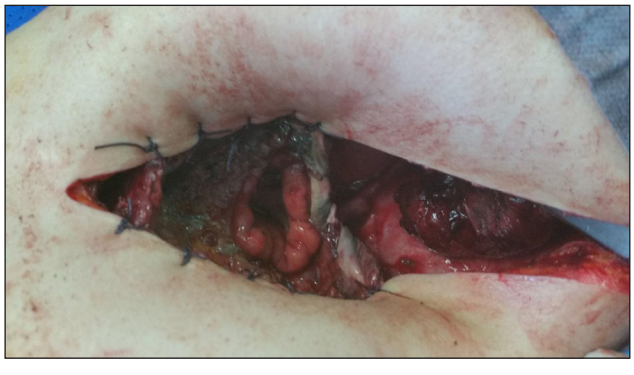

Fig. 6. A postoperative view after Eloesser open-flap formation. *Left*, a defect of the fundus is visible in the centre of eroded left diapfragm; *right*, the lower lobe of the left lung

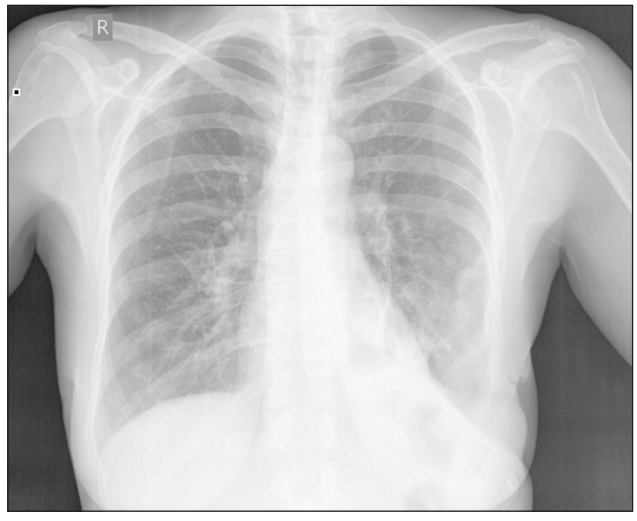

Fig. 7. Chest radiograph taken seven months after the first operation (15 December 2015). Just a small area of parenchymal consolidation can be seen in the left lung

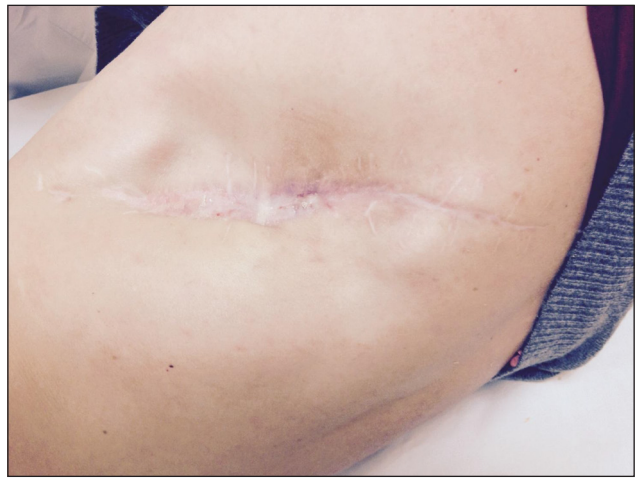

Fig. 8. A postoperative view of the chest wall seven months after the first surgical procedure

DISCUSSION

Invasive pulmonary fungal infections (IFI) are frequently a lethal complication of hematologic malignancies and occur after both conventional chemotherapy and bone marrow transplantation (BMT), as well as in untreated severely neutropenic patients. The incidence of IFI is increasing (1). The place of surgical interventions in such a group of patients is controversial. There are some publications concerning the value of pulmonary resection in hematologic patients who developed invasive pulmonary aspergillosis (9, 12, 13). Bernard (13) informed about 19 patients who were operated. Eight patients underwent emergency operations, before marrow recovery, to prevent massive hemoptysis. A lobectomy was performed in all cases. There was one postoperative death due to extensive aspergillosis. Seven patients were treated by elective resection of the residual mass. In the remaining four patients, surgical resection was performed as a diagnostic procedure. There were no postoperative deaths in this group of patients. The authors conclude that the combination of antifungal agents and surgical resection is an efficient strategy for the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancy. Chretien (9) presents 50 haematological patients (22-year data) with IFI (invasive fungal infection) who underwent pulmonary resection. In 27 cases, it was an emergency procedure to avoid hemoptysis. At the time of surgery, 30% of patients were still neutropenic and 54% required platelet transfusion. Lobectomy or segmentectomy were performed in 80% and 20% of cases, respectively. Mortality at 30 and 90 days post-surgery was 6% and 10%, respectively. After surgery, median overall survival was 21 months.

Surgery is a feasible and valuable option in haematological patients with IFI, because it is associated with a low incidence of complications. In selected cases, lung resection should be performed in haematological patients with IFI in order to avoid possibly fatal complications.

CONCLUSIONS

We report what is, to the best of our knowledge, the first case of invasive fungal infection (*Geotrichum capitatum*) successfully treated with intravenous amphotericin B, voriconazole and infected soft tissues (organs) surgery for the patient with multiple myeloma in prolonged neutropenia. The efficacy and safety of the surgery for infected soft tissues requires further evaluation.

Invasive fungal infection (IFI) is a recognized consequence of an immunocompromised state, but there are many possible underlying causes. These include neutropenia, exposure to high-dose corticosteroids, the presence of intravascular catheters, and prolonged exposure to broad-spectrum antibiotics.

Regardless, in our patient's case prolonged febrile neutropenia and the lung IFI persisted despite 20 days of intravenous micafungin. Pathological changes in the lungs remained despite treatment with intravenous micafungin.

We believe that in the case of our patient the systemic treatment alone was inadequate, and hypothesize that the use of the combination with surgery accounted for our patient's clinical improvement. In selected cases, lung resection should be performed in haematological patients with IFI in order to avoid possibly fatal complications.

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References

1. Gadea I, Cuenca-Estrella M, Prieto E, et al. Genotyping and antifungal susceptibility profile of Dipodascus capitatus isolates causing disseminated infection in seven hematological patients of a tertiary hospital. J Clin Microbiol. 2004; 42: 1832–6.
2. García-Ruiz JC, López-Soria L, Olazábal I, Amutio E, Arrieta-Aguirre I, Velasco-Benito V, Pontón J, Moragues MD. Invasive infections caused by Saprochaete capitata in patients with haematological malignancies: report of five cases and review of the antifungal therapy. Rev Iberoam Micol. 2013 Oct–Dec; 30(4): 248–55. doi: 10.1016/j.riam.2013.02.004. Epub 2013 Apr 11.
3. Arendrup MC, Boekhout T, Akova M, Meis JF, Cornely OA. Lortholary and on behalf of the ESCMID EFISG study group and ECMM. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast

infections. Clin Microbiol Infect. 2014; 20 (Suppl. 3): 76–98.
4. Gadea I, Cuenca-Estrella M, Prieto E, et al. Genotyping and antifungal susceptibility profile of Dipodascus capitatus isolates causing disseminated infection in seven hematological patients of a tertiary hospital. J Clin Microbiol. 2004; 42: 1832–6.
5. Cofrancesco E, Viviani MA, Boschetti C, Tortorano AM, Balzani A, Castagnone D. Treatment of chronic disseminated Geotrichum capitatum infection with high cumulative dose of colloidal amphotericin B and itraconazole in a leukaemia patient. Mycoses. 1995; 38: 377–84.
6. DeMaio J, Colman L. The use of adjuvant interferon-c therapy for hepatosplenic Blastoschizomyces capitatus infection in a patient with leukemia. Clin Infect Dis. 2000; 31: 822–4.
7. Blimark C, Holmberg E, Mellqvist UH, Landgren O, Björkholm M, Hultcrantz M, Kjellander C, Turesson I, Kristinsson SY. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica January 2015; 100: 107–13; Doi:10.3324/haematol.2014.107714
8. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis. (2009); 49(8): 1211–25. doi: 10.1086/605664.
9. Chretien ML, Legouge C, Pages PB, et al. Emergency and elective pulmonary surgical resection in haematological patients with invasive fungal infections: a report of 50 cases in a single centre. Clin Microbiol Infect. 2016 Jan 21.
10. Doumit M, Doumit G, Shamji FM, Gregorie S, Seppala RE. Gastropulmonary fistula after bariatric surgery. Can J Gastroenterol. 2009 Mar; 23(3): 215–6.
11. Liu B, Mi RH, Wei XD, Chen L, Ai H, Yuan FF, Yin QS, Song YP. Clinical analysis of ground glass opacity on CT as the first change of lung infection accompanied by haematologic malignancies. Zhonghua Yi Xue Za Zhi. 2016 Jan 19; 96(3): 163–6.
12. Cesaro S, Pegoraro A, Tridello G, Pillon M, Cannata E, Faggin S, Seccetto G. The role of surgery in the treatment of invasive fungal infection in paediatric haematology patients: a retrospective single-centre survey. Mycoses. 2014 Jul; 57(7): 394–9.
13. Bernard A, Caillot D, Couaillier JF, Cassanovas O, Guy H, Favre JP. Surgical management of invasive pulmonary aspergillosis in neutropenic patients. Ann Thorac Surg. 1997; 64: 1441–7.

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GASTROPULMONINĖ JUNGTIS DĖL GRYBELINĖS INFEKCIJOS PO CHEMOTERAPIJOS IR KAMIENINIŲ LĄSTELIŲ PERSODINIMO. SĖKMINGO GYDYMO ATVEJIS

Santrauka

Aktualumas. Invazyvi grybelinė plaučių infekcija gana dažnai komplikuoja chemopreparatais gydomų hematologinių ligonių gydymo eigą. Jos sukeltos komplikacijos kartais reikalauja skubaus chirurginio sprendimo. Viena iš tokių retų komplikacijų – susidariusi gastropulmoninė jungtis.

Ligonis ir metodai. Pateikiama ligonės, trejus metus gydytos dėl mielominės ligos chemopreparatais ir kamieninių ląstelių persodinimu, ligos istorijos analizė. Ligonę gydant atsirado grybelinės infekcijos židiniai kairiajame plautyje, kurie komplikavosi gastropulmonine jungtimi. Dėl šios komplikacijos bendra būklė blogėjo, todėl nuspręsta moterį operuoti. Per pirmąją operaciją, rezekavus du šonkaulius, buvo padaryta kairė pleurostoma, kurios dugne rastas į pleuros ertmę patekęs ir prairęs skrandžio dugnas. Taip pat buvo pašalinti 2 suirę kairiojo plaučio apatinės skilties segmentai. Žaizda tamponuota ir palikta gyti atvirai. Per kitas 4 savaites ligonė buvo gydoma specifiniais antibiotikais ir kasdieniniais perrišimais. Jos būklė pagerėjo, ligonė operuota pakartotinai. Operuojant skrandis atskirtas nuo diafragmos kraštų ir užsiūtas. Iš transponuotų priekinio dantytojo ir nugaros plačiojo raumenų sukurta nauja diafragma, kuria padengtas buvęs jos defektas. Pleurostoma palikta gyti atvirai dėl keleto bronchopleurinių fistulių. Žaizda visiškai sugijo per 6 mėnesius.

Išvados. Hematologiniai ligoniai, kuriems gydymo metu atsiranda invazyvios grybelinės infekcijos židinių plaučiuose, turėtų būti konsultuojami krūtinės chirurgo dėl galimos radikalios plaučio operacijos. Atsiradus šios ligos komplikacijoms – gastropulmoninei jungčiai – vienintelė išeitis yra aktyvus chirurginis gydymas, kuris šiai ligonei išgelbėjo gyvybę.

Raktažodžiai: invazyvi grybelinė infekcija po chemoterapijos, plaučių rezekcija, įgyta gastropulmoninė jungtis