Case Report
Volume 4:3, 2020
DOI: 10.37421/cmcr.2020.04.135

Clinical and Medical Case Reports

Open Access

Alsolated Aspergillosis of Biliary Tract in a Patient with Both Solid Organ Transplantation and Haematological Malignancy–A Case Report

Rosario Di Maggio[1], Giuseppina Calvaruso[1], Disma Renda[1], Veronica Di Salvo[1], Antonella Vulcano[2], Barbara Bartolini[2], Emiliano Maresi[3], Aroldo Gabriele Rizzo[4] and Aurelio Maggio[1]

[1]*Campus of Haematology Franco and Piera Cutino, AOOR Villa Sofia-V. Cervello, Palermo, Italy.*

[2]*Laboratory of Microbiology, National Institute for Infectious Diseases "L. Spallanzani", Rome, Italy.*

[3]*UOD of Autoptic Diagnosis, Department Promise, University of Palermo, Italy.*

[4]*Unit of Pathology, AOOR Villa Sofia-V. Cervello, Palermo, Italy.*

Abstract

Aspergillus is a ubiquitous mould that can cause a wide variety of clinical syndromes ranging from mere colonization to fulminant invasive disease. Invasive aspergillosis (IA) is the most severe presentation of aspergillosis. The lung is usually the portal of entry, from which the pathogen may disseminate to almost any organ, often the brain and skin. The diagnosis remains a significant challenge. IA is generally encountered in immunocompromised patients with steroid treatment, chemotherapy resulting in severe neutropenia, hematopoietic stem cell, and solid organ transplantation. We reported a case of aspergillosis presented as cholangitis, with no lung involvement, in a patient with history of kidney transplantation and recent Diagnosis of Large B-Cell Lymphoma (DLBCL). The patient had several predisposing factors, such as immunosuppressive drug therapy and steroid therapy. The patient died 50 days after a diagnostic splenectomy for DLBCL. The Polymerase Chain Reaction (PCR) assessment performed on biopsy specimen from duodenum was positive for Aspergillus spp.

It is a case of rare, isolated aspergillosis of biliary tract in a patient with both solid organ transplantation and haematological malignancy.

Keywords: Aspergillosis• Biliary tract• Transplantation• Haematological malignancy

Introduction

Aspergillus can cause a wide variety of clinical syndromes, ranging from mere colonization to fulminant invasive disease. Mortality due to documented invasive aspergillosis approaches 80% to 100% in high-risk patients, including those with underlying hematologic malignancy or bone marrow or solid organ transplantation [1]. Aspergillus fumigatus is the most common cause of human aspergillosis, being responsible for about 90% of cases [2]. The next most recovered species are Aspergillus flavus, Aspergillus Niger, and Aspergillus Terreus.

In immunocompromised patients, outbreaks have usually been associated with construction activities as invasive pulmonary aspergillosis [3]. Moreover, fungal infections of the biliary tract are uncommon and usually caused by Candida spp., which have been reported to cause biliary obstruction and cholangitis even in immunocompetent host [1]. In particular isolated aspergillosis of intestinal and biliary tract is rare, and the diagnosis is extremely difficult, since blood cultures usually remain negative [4,5]. Here we reported a case of aspergillosis presented as isolated cholangitis in a patient with history of kidney transplantation and recent DLBCL.

Case report

Clinical presentation

A 49-year-old woman was admitted to our Hospital in February 2018 due to pain in the left hypochondrium, severe anemia (Hb 7.7 g/dl), LDH increased levels and inhomogeneous splenomegaly (17 cm). A medical history of kidney transplantation in 2001 for contracted kidneys. After surgery an immunosuppressive therapy with tacrolimus was initiated.

Diagnostic assessments

A diagnosis of cold antibody hemolytic anemia (CAHA) was established through Coombs test (C3d3 positive). A steroid therapy with prednisone 1 mg/kg was prescribed.

Inhomogeneous splenomegaly was furtherly investigated through Positron Emission Tomography/Computed Tomography (PET-CT) assessment, resulting in the presence of two vascularized hypodense lesions with high metabolic activity on PET. Bone marrow aspirate and osteomyelobiopsia were performed for a lymphoproliferative disease suspect. Both assessments were negative for blood disorders.

Therefore, splenectomy was indicated as following step. Before surgery, liver function test was performed, showing 38/254 IU/L for AST/ALT respectively, 239 IU/L for gamma-GT. Moreover, preoperative abdomen echo revealed: liver modestly increased in volume, slightly hyperechoic; gallbladder gallstones; patent intra and extrahepatic biliary tracts; spinal portal axis of regular caliber. Negative abdominal CT with contrast medium. In addition, a treatment with ciprofloxacin was provided to the patient before surgery.

Splenectomy was performed on 14 March 2018: no obstructive jaundice was observed; however, Monomorphic Post-transplant Lymphoproliferative Disorder (PTLD) type was confirmed by the histologic assessment (immunohistochemistry) and it was compatible with diffuse Large B-Cell Lymphoma. For the postoperative course, patient was transferred to our hematology unit.

Follow-up and outcomes

In the postoperative period, patient received a total parenteral nutrition. After surgery, worsening of patient clinical conditions occurred: hyperpyrexia, pulse oximetry reduction, left pleural effusion and right perihilar thickening evidence at a radiologic assessment (X-Ray).

***Address for Correspondence :** Dr. Rosario Di Maggio, Campus of Haematology Franco and Piera Cutino, AOOR Villa Sofia-V. Cervello, Palermo, Italy, Mobile: +39 320.0544341, Email: rdm83@hotmail.it*

Received 20 July, 2020; **Accepted** 10 October, 2020; **Published** 17 October, 2020

Abdominal CT was performed which showed splenic vein thrombosis, for which an anticoagulation treatment was initiated. Therapy with tacrolimus was suspended and antibiotic therapy was initiated with quinolones and carbapenems.

From 20 March 2018 biochemical profile showed a progressive increase of direct bilirubin up to 30 mg/dl: transaminases over 5xN, LDH 3000 U/L and creatinine 2.4 mg/dl). Moreover, hyperpyrexia was persistent at 39°C.

Blood cultures, pharyngeal swab and urine cultures were performed but no microorganism was isolated. In addition, serological investigations and polymerase chain reaction (PCR) tests for Cytomegalovirus (CMV), Epstein-Barr (EBV), hepatitis C virus (HCV), Hepatitis B Virus (HBV), Human Herpes Virus 6 (HHV-6) were negative.

Despite antibiotic treatment and due to the worsening of clinical condition and hyperpyrexia persistence, the following additional therapies were initiated: linezolid and fluconazole first, then cephalosporins and aminoglycosides.

The abdominal echocolor doppler examination and chest-abdomen CT with contrast medium with exclusion of intestinal ischemia or extension of splenic thrombosis. The presence of marked gastrectasis with abundant liquid content was observed.

Due to progressive reduction of hemoglobin and platelets levels, treatment with steroids was reintroduced.

High-dose steroid therapy and rituximab were initiated, on the hypothesis of lupus hepatitis or multi-organ damage consequent to immune system dysfunction.

Deteriorating clinical conditions occurred with liver function worsening and progressive severe respiratory failure. Cardio-respiratory insufficiency led to patient death on 03 May 2018.

Diagnosis post-mortem

The patient underwent a diagnostic autopsy a few days after her death.

Results

Macroscopy

At the opening of the abdominal cavity abundant blood serum effusion, focal peritoneal adhesions associated with multiple petechiae, partly confluent, involving the omentum, peritoneal, visceral and parietal serous. Greenish-colored liver with sharp edges weighing 1950gr.

Microscopy

Liver: widespread intra-hepatocyte cholestasis associated with the presence of bile cylinders and chronic cholangiolitis, focal portal fibrosis and microvesicular steatosis of the hepatocytes.

The portal inflammatory process extends focally to the periportal hepatocytes. Micro hemorrhages of the portal space. Hepatocyte necrosis partly autolytic.

Duodenum: suppurative acute duodenitis from Candida albicans.

PCR

Molecular investigation: formalin-fixed and paraffin-embedded duodenum and samples were sliced (sections, 5-10 mm), deparaffinated once with 1 ml xylol and twice with 1 ml ethanol 100% [6]. After drying of the tissue, an additional pre-incubation step was added, using exposure to lysozyme buffer at 37°C for 1h, to increase the yield of the extraction protocol. DNA was extracted in the robotic workstation QIAcube using QIAamp® DNA Mini Kit (QIAGEN, UK) and eluted in 50 µl AE buffer.

DNA was examined for the identification the mitochondrial DNA of Aspergillus sp [6] and fungal pathogens [7] using in house PCR targeting. Moreover, a pan-Fungal PCR targeting the 28s rDNA gene, followed by the amplicon sequencing were performed.

The results of pathogen molecular testing are summarized in Table1. The molecular tests performed on duodenal samples were negative for pan-Fungal, while Aspergillus spp. was identified in one sample (Id. 14-19-/18) (Table 1).

Discussion

IA caused by the fungus Aspergillus spp. (specifically by Aspergillus fumigatus) is a frequent and life-threatening complication of chemotherapy and bone marrow transplantation with high rates of mortality and morbidity [8]. The lung is usually the portal of entry, from which the pathogen may disseminate to almost any organ, often the brain and skin [4]. Moreover, fungal infections of the biliary tract are uncommon, in particular the isolated form [4,5].

To our knowledge, the described case report is a rare situation of isolated aspergillosis of biliary tract in a patient with a clinical history of kidney transplantation and with large B-cell lymphoma. Diagnosis of aspergillosis is crucial to avoid a life-threatening situation. Traditional microbiological methods (culture of clinical samples and direct microscopy) have low sensitivity and do not help to discriminate between infection and colonization and may only give positive results at late stages of the disease. Furthermore, in some cases, the underlying condition of the patient prevents the use of invasive techniques to obtain suitable clinical samples. For these reasons, methods for the detection of different circulating markers (e.g. fungal cell wall components and genomic fungal DNA) have been developed in recent years [4].

The use of serological tests of blood or other fluids (e.g. serum, urine and bronchoalveolar lavage fluid) in the diagnosis of IA is the focus of ongoing clinical investigations. Aspergillus galactomannan and (1 fi 3)-βglucan are two markers of special interest [4].

Diagnosis of isolated aspergillosis is a greater challenge as it could be obtained with the analysis of biopsy samples. For patients, as the one described here, with negative results for blood, swap and urine culture, the diagnosis should be done on the basis of a combination of compatible clinical findings, risk-factors (including therapies), radiological data. Anyway, more sensitive diagnostic tests to detect the early onset of aspergillosis isolated form should be developed; this could support the definition of a stronger rational for the most appropriate antifungal drugs administration.

Regarding treatment, we proceeded with a combination of therapies - linezolid and fluconazole first, cephalosporins and aminoglycosides subsequently-in order to cover the widest spectrum of microorganisms. This strategy was defined based on clinical conditions, patient's risk factors and radiologic assessment results. In patients with several risk factors, the early antifungal treatment should be indeed considered even when the biopsy cannot be performed.

Table 1: Results of pathogen detection by molecular testing on the different duodenal sample types.

Pathogen	ID. Tissue	Result
Pn-Fungal	Id. 14-19-/18	Neg
Pn-Fungal	Id. 14-20-/18	Neg
Pn-Fungal	Id. 14-26-/18	Neg
Aspergillus spp	Id. 14-19-/18	Pos
Aspergillus spp	Id. 14-20-/18	Neg
Aspergillus spp	Id. 14-26-/18	Neg

Pn-Fungal: Pan-Fungal; ID: identification code; Neg: Negative; Pos: Positive.

Between antifungal treatments, a prophylaxis with fluconazole has been described to significantly reduce invasive fungal infections in transplant recipients, in the early postoperative period [1]. Anyway, resistance to the triazoles in the main pathogenic species Aspergillus fumigatus has been reported in an increasing number of countries [9]. Some other authors suggested that the administration of L-AmpB in high-risk patients is independently associated with a reduction of invasive fungal infections [10].

The successful therapy could depend on both early diagnoses, despite it is difficult to establish, and defects of immune system of the host, such as neutropenia or high-dose immunosuppressive therapy.

Acknowledgement

Additional support for our research was provided by Foundation Franco and Piera Cutino.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1. Chen, Yuchong. Zhu, Dingheng. Yuan, Zhizhong and Yu, Hongyu. et al. "Aspergillosis of Biliary Tract After Liver Transplantation: A Case Report." *Mycopathologia.* 170(2010): 117–121.
2. David W, Warnock. Rana A, Hajjeh and Brent A, Lasker. "Epidemiology and prevention of invasive aspergillosis." *Curr Infect Dis Rep.* 3(2001): 507.
3. Shivaprakash M, Rudramurthy. Raees A, Paul. Arunaloke, Chakrabarti and Johan W. Mouton. et al. "Invasive Aspergillosis by Aspergillus flavus: Epidemiology, Diagnosis, Antifungal Resistance, and Management." *J. Fungi.* 5(2019): 55.
4. Munoz, P. Guinea, J and Bouza, E. "Update on invasive aspergillosis: clinical and diagnostic aspects." *Clin Microbiol Infect.* 12(2006): 24–39.
5. Ioannis, Koutsounas and Emmanouil, Pyleris. "Isolated enteric aspergillosis in a non-severely immunocompromised patient. Case report and literature review." *Arab J Gastroenterol*. 16(2015): 72-75.
6. Bialek, Ralf. Feucht, Antje. Aepinus, Christian and Gudrun, Just-Nübling. et al. "Evaluation of two nested PCR assays for the detection of Histoplasma capsulatum DNA in human tissue." *J Clin Microbiol*. 40(2002): 1644-1647.
7. Sandhu, GS. Kline, BC. Stockman, L and Roberts, GD. et al. "Molecular probes for diagnosis of fungal infections." *J Clin Microbiol.* 33(1995): 2913-2919.
8. Thornton, CR. "Detection of Invasive Aspergillosis. Advances in Applied Microbiology". 70(2010): 187-216.
9. "National Guidelines for the Prevention of Nosocomial Aspergillosis." 2018.
10. Jesus, Fortún. Pilar, Martín-Davila. Santiago, Moreno and Rafael, Barcena. et al. "Prevention of invasive fungal infections in liver transplant recipients: the role of prophylaxis with lipid formulations of amphotericin B in high-risk patients." *J Antimicrob Chemother*. 52(2003): 813-819.

How to cite this article: Rosario Di Maggio, Giuseppina Calvaruso, Disma Renda, Veronica Di Salvo, Antonella Vulcano, et al. Isolated Aspergillosis of Biliary Tract in a Patient with Both Solid Organ Transplantation and Haematological Malignancy–A Case Report. Clin Med Case Rep 4 (2020):135. doi: 10.37421/cmcr.2020.04.135