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Case Report

Pneumocystis jirovecii pneumonia in patients with decompensated cirrhosis: a case series

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ABSTRACT

Objectives: *Pneumocystis jirovecii* pneumonia (PCP) incidence is increasing in people without HIV. Decompensated liver cirrhosis is not currently considered a risk factor for PCP. The aim of this paper is to describe a case series of patients with decompensated liver cirrhosis and PCP.

Methods: All consecutive patients hospitalized with decompensated cirrhosis and microbiology-confirmed PCP at Policlinico Modena University Hospital from January 1, 2016 to December 31, 2021 were included in our series.

Results: Eight patients were included. All patients had advanced-stage liver disease with a model for end-stage liver disease score above 15 (6/8 above 20). Four were on an active orthotopic liver transplant waiting list at the time of PCP diagnosis. Five patients did not have any traditional risk factor for PCP, whereas the other three were on glucocorticoid treatment for acute-on-chronic liver failure. All patients were treated with cotrimoxazole, except two who died before the diagnosis. Five patients died (62.5%), four of them within 30 days from PCP diagnosis. Of the remaining three, one patient underwent liver transplantation.

Conclusion: Although further studies are needed, liver cirrhosis can be an independent risk factor for PCP in patients with decompensated cirrhosis that is mainly due to severe alcoholic hepatitis and who are on corticosteroids therapy, and primary prophylaxis for PCP should be considered.

Introduction

Pneumocystis jirovecii pneumonia (PCP) is an opportunistic fungal infection that can be life-threatening, but it is preventable and treatable if diagnosed in time [1,2]. In recent years, risk factors other than HIV have been identified, including glucocorticoid therapy, lymphopenia, hematologic malignancies, solid organ transplantations, and autoimmune diseases [2–4]. Patients with end-stage liver cirrhosis experience a significant impairment of the immune system called cirrhosis-associated immune dysfunction. This multifactorial entity, caused by an interplay of splenic pooling of immune system cells, hypersplenism, and increased gut permeability [5], may lead to an exhaustion of the immune function.

Liver cirrhosis is not considered a classical risk factor for PCP, and only a few cases of PCP in this population were described [6–9]. In this study, we present a case series of patients with decompensated liver cirrhosis and PCP.

Patients and methods

Patients hospitalized with decompensated cirrhosis and microbiology-confirmed PCP at Azienda Ospedaliero-Universitaria

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Policlinico Modena from January 1, 2016 to December 31, 2021 were included.

Microbiological identification of *P. jirovecii* was defined as either a positive polymerase chain reaction (PCR) or a positive immunofluorescence test for *P. jirovecii* on bronco-alveolar lavage (BAL). Patients with positive PCR but negative immunofluorescence and serum (1,3)-β-D-glucan, no symptoms, or symptoms improved without PCP specific treatment were considered as colonized and were excluded. For patients for whom quantitative PCR was available (Supplementary Materials), thresholds proposed by Damiani *et al.* [10] were used.

Clinical data and outcomes were collected retrospectively using electronic clinical records.

Results

Eight patients with end-stage liver disease diagnosed with PCP were included. A cirrhosis complication (acute hepatic decompensation, encephalopathy, hepatocellular carcinoma, or hepato-renal syndrome) was the most frequent reason for hospital admission, whereas septic shock was reported in one patient.

Table 1 shows patient baseline characteristics, clinical presentation, microbiological diagnosis, PCP therapies, and outcomes. No patients had COVID-19 before PCP. Half the patients were on an active liver transplant waiting list at PCP diagnosis. Six patients had alcohol-related liver cirrhosis, and three were on glucocorticoid treatment for acute-on-chronic liver failure before PCP diagnosis.

All included patients had clinical and radiologic characteristics at computed tomography (CT) scans consistent with PCP. Only one patient was on primary prophylaxis for PCP, implemented just 6 days before diagnosis.

Regarding co-infections, patient 1 had a concomitant extended-spectrum β-lactamases + *Enterobacter cloacae* and *Bacillus cereus* peritonitis, treated with piperacillin/tazobactam and tigecycline. Patient 5 had a concomitant probable pulmonary aspergillosis (*Aspergillus fumigatus* isolation from BAL culture, positive aspergillus PCR, and positive serum galactomannan [GM] plus compatible images at pulmonary CT scans). BAL was performed the day before the patient died, and the results arrived after death; thus, no therapy for aspergillosis or PCP was started. Patients 6 and 8 had a concomitant probable pulmonary aspergillosis (positive GM and PCR on BAL for patient 6 and *A. fumigatus* isolation from BAL culture for patient 8, plus compatible CT imaging), treated with voriconazole. Patient 7 had a probable concomitant cytomegalovirus-pneumonia with 12,667 copies/ml on BAL after acute respiratory distress syndrome development. Ganciclovir was prescribed.

Five patients died (62.5%), four of them within 30 days from PCP diagnosis, and of the remaining three, one patient underwent liver transplantation.

Conclusion

To our knowledge, this is the largest case series describing PCP in patients with decompensated liver cirrhosis. On the basis of the outcomes in our series, not only should this infection be included among differential diagnoses, but primary prophylaxis for PCP should be considered, especially if the patient is on corticosteroids therapy.

We have found four case reports and a case series describing PCP in patients with decompensated cirrhosis and no other classical PCP risk factors [6–9] (Supplementary Materials, Table 2). The case series by Faria *et al.* [7] describes seven patients with severe alcoholic hepatitis and PCP, six of whom received corticosteroids

Table 1
Baseline characteristics, type of diagnosis, therapy, and outcomes of the eight patients with decompensated cirrhosis who were diagnosed with PCP at Policlinico Modena University Hospital from 2016 to 2021.

Patient	Sex/age	Symptoms	Charlson's score	Liver failure etiology	Child/model for end-stage liver disease score	In orthotopic liver transplant list	Steroid therapy for acute-on-chronic liver failure	Total lymphocyte count migl/mmc	(1,3)-β-d-glucan (pg/ml)	Type of microbiological diagnosis	1st/2nd line Tp	Steroids	Concomitant coinfection	Ventilation	Intensive care unit	Transplant	Days of Tp	Outcome	Days from PCP diagnosis to death	Cause of death
1	M/56	Fever, dyspnea	4	Alcohol	C10/19	Yes	No	0.91	524	PCR	TMP-SMX	No	*E. cloacae, B. cereus* Peritonitis	Yes	Yes	No	5	Death	5	MOF in septic shock
2	M/81	Fever, cough	10	Metabolic	C11/35	No	No	Not available	46	PCR	/	No	No	No	No	No	0	Death	0	Esophageal varices bleeding
3	M/52	Fever, dyspnea	8	Alcohol, metabolic	C12/34	Yes	No	1.7	468	PCR	TMP-SMX/CLM+PRI	Yes	No	No	No	No	12	Death	99	Hematemesis and hemoperitoneum
4	F/52	Fever	5	Alcohol	C/29	No	Yes (Dexamethasone 8 mg/day)	0.56	524	PCR + immunofluorescence	TMP-SMX	Yes	No	Yes	Yes	No	27	Death	26	MOF in septic shock
5	F/66	Fever, drowsiness	5	HBV infection, alcohol	C12/24	No	No	1.11	269	PCR	/	Yes	Probable pulmonary aspergillosis	Yes	Yes	No	0	Death	0	Aspergillosis and encephalopathy
6	M/58	Fever, drowsiness	3	Alcohol, metabolic	B9/19	No	Methylprednisolone 40 mg/day	1.67	524	PCR	TMP-SMX/CLM+PRI	Yes	Probable pulmonary aspergillosis	No	No	No	24	Clinical cure /	/	/
7	M/34	Fever, dyspnea	2	Alcohol	C10/29	Yes	No	1.9	16	PCR (33,585 cp/ml)	TMP-SMX	Yes	Cytomegalovirus pneumonia	Yes	Yes	Yes	21	Clinical cure /	/	/
8	F/63	Dyspnea	6	HBV-HDV infection	C11/44	Yes	Yes (Dexamethasone 6 mg twice a day)	0.25	701	PCR (2673 cp/ml)	TMP-SMX	Yes	Probable pulmonary aspergillosis (1 week later)	No	Yes	Yes	21	Clinical cure /	/	/

CLM+PRI: clindamycin + primaquine; F, female; M, male; MOF, multiple organ failure; PCP, *Pneumocystis jirovecii* pneumonia; PCR, polymerase chain reaction; TMP-SMX: trimethoprim-sulfamethoxazole; Tp: therapy.

for liver failure for at least 6 days before respiratory distress. Notably, in our series, although three of eight patients were on corticosteroid therapy at the diagnosis, the remaining five patients had no traditional risk factors for PCP.

These findings are consistent with the idea that decompensated cirrhosis itself can be considered a cause of acquired immunodeficiency [11]. In fact, the impairment of T cell-mediated immunity in patients with liver failure is particularly evident in the subset of patients with severe alcoholic hepatitis who show higher interleukin-10 levels and lower interferon-γ production [5]. Moreover, glucocorticoids therapy, often used in patients with acute-on-chronic liver failure because it reduces short-term mortality [12], is a well-known risk factor for PCP [1,2]. For this reason, in these patients, we could encourage shortening corticosteroid treatment duration when possible. For example, as recently suggested, the Lille score could help reduce glucocorticoid therapy from 7 to 4 days in non-responder cases [13].

In this population, PCP might often be misdiagnosed, and there might be some relevant diagnostic delay, mainly because decompensated cirrhosis is not considered a traditional risk factor for PCP and there could be other causes of respiratory insufficiency. Indeed, in our case series, PCP was not immediately suspected, and once it was, patients had to undergo BAL; thus, median time to diagnosis reached 24 days, and in two cases, results arrived post mortem.

Our patients were extremely fragile, and the high mortality rate reported could be related not only to PCP but also to concomitant infections and/or transplant delay because they had a high model for end-stage liver disease score at baseline (median 26.5), and five of eight had other infections at diagnosis.

This study has several limitations, mainly due to its retrospective nature; thus, a few data such as lymphocyte subpopulations are not available. Furthermore, no standardized screening protocol was in place for the early identification of PCP, potentially leading to under-diagnosing. Finally, the efficacy and safety of PCP prophylaxis cannot be determined. Nevertheless, our study has some strengths. Indeed, we believe it is the largest case series of patients with PCP and end-stage liver disease. We acknowledge that the total number of cases described in the literature, including ours, is approximately 20, but infectious complications in this population are largely underestimated, and further studies are needed. In conclusion, this case series suggests that in hospitalized patients with decompensated cirrhosis mainly due to severe alcoholic hepatitis and on corticosteroids therapy, PCP should be included among differential diagnoses, and eventually, primary prophylaxis should be considered.

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Ethical approval

Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Author contributions

Study concept: Erica Franceschini, Cristina Mussini. Study design and data collection: Erica Franceschini, Giovanni Dolci, Antonella Santoro, Alice Riccò, Marianna Menozzi, Giulia Jole Burastero, Biagio Cuffari, Nicola De Maria, Lucia Serio, Fabrizio Di Benedetto, Massimo Girardis, Cristina Mussini. Data interpretation: Erica Franceschini, Giovanni Dolci, Nicola De Maria, Antonio Colecchia, Giulia Jole Burastero, Cristina Mussini. First draft: Erica Franceschini, Giovanni Dolci. Critical revision for important intellectual content: Erica Franceschini, Giovanni Dolci, Marianna Meschiari, Alice Riccò, Marianna Menozzi, Giulia Jole Burastero, Biagio Cuffari, Nicola De Maria, Lucia Serio, Emanuela Biagioni, Stefano Di Sandro, Antonio Colecchia, Massimo Girardis, Fabrizio Di Benedetto, Cristina Mussini.

Declarations of competing interest

The authors have no competing interests to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.12.027.

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