

World Journal of *Clinical Cases*

World J Clin Cases 2022 March 26; 10(9): 2660-2975



REVIEW

- 2660 Role of metabolites derived from gut microbiota in inflammatory bowel disease
Zheng L, Wen XL, Duan SL

MINIREVIEWS

- 2678 Roles of Wnt/ β -catenin signaling pathway related microRNAs in esophageal cancer
Chu CY, Wang R, Liu XL
- 2687 Animal models applied to acute-on-chronic liver failure: Are new models required to understand the human condition?
Gama JFG, Cardoso LMDF, Lagrota-Candido JM, Alves LA

ORIGINAL ARTICLE**Case Control Study**

- 2700 Associations between coagulation factor XII, coagulation factor XI, and stability of venous thromboembolism: A case-control study
Meng Y, Li Y, Ye YJ, Ma Q, Zhang JB, Qin H, Deng YY, Tian HY

Retrospective Cohort Study

- 2710 Nomogram to predict the risk of endoscopic removal failure with forceps/baskets for treating submandibular stones
Huang Y, Liang PS, Yang YC, Cai WX, Tao Q
- 2721 Association between anesthesia technique and complications after hip surgery in the elderly population
Guo LS, Wang LN, Xiao JB, Zhong M, Zhao GF

Retrospective Study

- 2733 Perforating and nonperforating indications in repeated surgeries for Crohn's disease
Shen WS, Huang XH, Liu RQ, Li CY, Li Y, Zhu WM
- 2743 Treatment of *Pneumocystis jirovecii* pneumonia in non-human immunodeficiency virus-infected patients using a combination of trimethoprim-sulfamethoxazole and caspofungin
Wu HH, Fang SY, Chen YX, Feng LF
- 2751 Acute kidney injury in traumatic brain injury intensive care unit patients
Huang ZY, Liu Y, Huang HF, Huang SH, Wang JX, Tian JF, Zeng WX, Lv RG, Jiang S, Gao JL, Gao Y, Yu XX
- 2764 Enucleation combined with guided bone regeneration in small and medium-sized odontogenic jaw cysts
Cao YT, Gu QH, Wang YW, Jiang Q

Clinical Trials Study

- 2773 Determination of the ED₉₅ of intranasal sufentanil combined with intranasal dexmedetomidine for moderate sedation during endoscopic ultrasonography

Zou Y, Li N, Shao LJZ, Liu FK, Xue FS, Tao X

Observational Study

- 2783 Overexpression of Ubiquilin4 is associated with poor prognosis in patients with cervical cancer

Wang LN, Huang KJ, Wang L, Cheng HY

Randomized Clinical Trial

- 2792 Peplau's interpersonal relationship theory combined with bladder function training on patients with prostate cancer

Yang XH, Wu LF, Yan XY, Zhou Y, Liu X

SYSTEMATIC REVIEWS

- 2801 Efficacy of bone grafts in jaw cystic lesions: A systematic review

Wang J, Yao QY, Zhu HY

CASE REPORT

- 2811 Short stature associated with a novel mutation in the aggrecan gene: A case report and literature review

Yin LP, Zheng HX, Zhu H

- 2818 Treatment with sorafenib plus camrelizumab after splenectomy for primary splenic angiosarcoma with liver metastasis: A case report and literature review

Pan D, Li TP, Xiong JH, Wang SB, Chen YX, Li JF, Xiao Q

- 2829 Sarcomatoid intrahepatic cholangiocarcinoma with good patient prognosis after treatment with Huaier granules following hepatectomy: A case report

Feng JY, Li XP, Wu ZY, Ying LP, Xin C, Dai ZZ, Shen Y, Wu YF

- 2836 Sequential occurrence of T790M mutation and small cell lung cancer transformation in EGFR-positive lung adenocarcinoma: A case report

Hong E, Chen XE, Mao J, Zhou JJ, Chen L, Xu JY, Tao W

- 2844 Early diagnosis of Gitelman syndrome in a young child: A case report

Wu CY, Tsai MH, Chen CC, Kao CH

- 2851 Congenital intestinal malrotation with gastric wall defects causing extensive gut necrosis and short gut syndrome: A case report

Wang Y, Gu Y, Ma D, Guo WX, Zhang YF

- 2858 Delusional parasitosis as premotor symptom of parkinson's disease: A case report

Oh M, Kim JW, Lee SM

- 2864** Laninamivir-induced ischemic enterocolitis: A case report
Suzuki C, Kenzaka T
- 2871** Intramural pregnancy after *in vitro* fertilization and embryo transfer: A case report
Xie QJ, Li X, Ni DY, Ji H, Zhao C, Ling XF
- 2878** Bilateral ureteral reimplantation in a patient with an intraperitoneal ectopic bipenis: A case report
Jia YT, Shi BL, Zhang J, Li YY, Zhu J
- 2883** Lumbar disc sequestration mimicking a tumor: Report of four cases and a literature review
Li ST, Zhang T, Shi XW, Liu H, Yang CW, Zhen P, Li SK
- 2895** Parasitic leiomyoma in the trocar site after laparoscopic myomectomy: A case report
Roh CK, Kwon HJ, Jung MJ
- 2901** Giant nontraumatic myositis ossificans in a child: A case report
Xia AN, Wang JS
- 2908** Paradoxical carbon dioxide embolism during laparoscopic hepatectomy without intracardiac shunt: A case report
Jeon S, Hong JM, Lee HJ, Kim Y, Kang H, Hwang BY, Lee D, Jung YH
- 2916** Local hyperthermia combined with chemotherapy for the treatment of multiple recurrences of *undifferentiated pleomorphic sarcoma*: A case report
Zhou YT, Wang RY, Zhang Y, Li DY, Yu J
- 2923** Acute coronary artery stent thrombosis caused by a spasm: A case report
Meng LP, Wang P, Peng F
- 2931** Turner syndrome with primary myelofibrosis, cirrhosis and ovarian cystic mass: A case report
Xu LW, Su YZ, Tao HF
- 2938** Esophageal myoepithelial carcinoma: Four case reports
Lu H, Zhao HP, Liu YY, Yu J, Wang R, Gao JB
- 2948** Ipsilateral hemifacial microsomia with dextrocardia and pulmonary hypoplasia: A case report
Guo R, Chang SH, Wang BQ, Zhang QG
- 2954** Upper gastrointestinal bleeding from a Mallory-Weiss tear associated with transesophageal echocardiography during successful cardiopulmonary resuscitation: A case report
Tang MM, Fang DF, Liu B
- 2961** Malignant struma ovarii with papillary carcinoma combined with retroperitoneal lymph node metastasis: A case report
Xiao W, Zhou JR, Chen D

- 2969** Occult colon cancer with sepsis as the primary manifestation identified by bone marrow puncture: A case report

Wang HJ, Zhou CJ

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Arunchai Chang, MD, Assistant Professor, Lecturer, Staff Physician, Division of Gastroenterology, Department of Internal Medicine, Hatyai Hospital, Hatyai 90110, Songkhla, Thailand. busmdcu58@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

March 26, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Retrospective Study

Treatment of *Pneumocystis jirovecii* pneumonia in non-human immunodeficiency virus-infected patients using a combination of trimethoprim-sulfamethoxazole and caspofungin

Huan-Huan Wu, Shuang-Yan Fang, Yan-Xiao Chen, Lan-Fang Feng

Specialty type: Infectious diseases**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0**P-Reviewer:** Brat K**Received:** August 24, 2021**Peer-review started:** August 24, 2021**First decision:** November 17, 2021**Revised:** November 19, 2021**Accepted:** February 15, 2022**Article in press:** February 15, 2022**Published online:** March 26, 2022**Huan-Huan Wu, Shuang-Yan Fang, Yan-Xiao Chen, Lan-Fang Feng**, Department of Respiratory Medicine, Dongyang Hospital Affiliated to Wenzhou Medical University, Dongyang 322100, Zhejiang Province, China**Corresponding author:** Huan-Huan Wu, MD, Doctor, Department of Respiratory Medicine, Dongyang Hospital Affiliated to Wenzhou Medical University, No. 60 Wuning West Road, Dongyang 322100, Zhejiang Province, China. huanhuan871002@163.com**Abstract****BACKGROUND**

Pneumocystis jirovecii pneumonia (PJP) is an infectious disease common in immunocompromised hosts. However, the currently, the clinical characteristics of non-HIV patients with PJP infection have not been fully elucidated.

AIM

To explore efficacy of trimethoprim-sulfamethoxazole (TMP-SMX) and caspofungin for treatment of non-human immunodeficiency virus (HIV)-infected PJP patients.

METHODS

A retrospective study enrolled 22 patients with non-HIV-infected PJP treated with TMP-SMX and caspofungin from 2019 to 2021. Clinical manifestations, treatment and prognosis of the patients were analyzed.

RESULTS

Five patients presented with comorbidity of autoimmune diseases, seven with lung cancer, four with lymphoma, two with organ transplantation and four with membranous nephropathy associated with use of immunosuppressive agents. The main clinical manifestations of patients were fever, dry cough, and progressive dyspnea. All patients presented with acute onset and respiratory failure. The most common imaging manifestation was ground glass opacity around the hilar, mainly in the upper lobe. All patients were diagnosed using next-generation sequencing, and were treated with a combination of TMP-SMX and caspofungin. Among them, 17 patients received short-term adjuvant glucocorticoid therapy. All patients recovered well and were discharged from hospital.

CONCLUSION

Non-HIV-infected PJP have rapid disease progression, high risk of respiratory failure, and high mortality. Combination of TMP-SMX and caspofungin can effectively treat severe non-HIV-infected PJP patients with respiratory failure.

Key Words: Acquired immunodeficiency syndrome; Non-human immunodeficiency virus-infected patients; Immunosuppression; caspofungin; Mortality; *Pneumocystis jirovecii* pneumonia

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: *Pneumocystis jirovecii* pneumonia (PJP) is common in immunocompromised hosts. However, the clinical characteristics of non-human immunodeficiency virus (HIV) infected PJP patients have not been fully elucidated. This was a retrospective study of non-HIV-infected PJP treated with trimethoprim-sulfamethoxazole (TMP-SMX) and caspofungin. Clinical manifestations, treatment and prognosis of the patients were evaluated. Non-HIV-infected PJP patients are characterized by rapid disease progression, high risk of respiratory failure, and high mortality. Early diagnosis and treatment can improve survival in non-HIV-infected PJP patients. The findings of the current study showed that combination of TMP-SMX and caspofungin is effective for non-HIV-infected PJP patients with respiratory failure.

Citation: Wu HH, Fang SY, Chen YX, Feng LF. Treatment of *Pneumocystis jirovecii* pneumonia in non-human immunodeficiency virus-infected patients using a combination of trimethoprim-sulfamethoxazole and caspofungin. *World J Clin Cases* 2022; 10(9): 2743-2750

URL: <https://www.wjgnet.com/2307-8960/full/v10/i9/2743.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i9.2743>

INTRODUCTION

Approximately 75% of patients infected with human immunodeficiency virus (HIV) positive present with *Pneumocystis jirovecii* pneumonia (PJP) during the early stages of the infection[1]. Technological advancements in medicine have led to development of effective therapies that have significantly reduced the incidence of PJP in patients with acquired immunodeficiency syndrome (AIDS). For example, the CD4⁺T lymphocyte counts have been shown to be accurate in identifying patients at high clinical risk of developing PJP[2]. In addition, prophylaxis interventions have been designed for patients at risk of PJP[3] and sensitive immunofluorescence detection methods are now available for timely detection. The development of combined antiretroviral therapy drugs has significantly reduced incidence of PJP and improved prognosis of HIV-positive PJP (HIV + PJP) patients[4]. Clinically, the number of non-HIV-infected PJP patients has been on the rise annually owing to the increased use of immunosuppressants and organ transplantations[5,6]. The mortality levels of non-HIV-infected PJP patients ranges between 30% and 60%, whereas the mortality of HIV + PJP patients ranges between 10% and 20%[7]. In comparison, management measures for non-HIV-infected PJP are not standardized as is the case for HIV + PJP patients. Moreover, the clinical attention for non-HIV-infected patients is poorer compared with that of HIV + PJP patients.

The aim of this retrospective study was to explore the characteristics of non-HIV-infected PJP treated with trimethoprim-sulfamethoxazole (TMP-SMX) and caspofungin. The findings of this study are expected to improve our understanding of the occurrence of PJP in non-HIV-infected patients, and thus prevent misdiagnosis and reduce mortality rate of non-HIV-infected PJP patients.

MATERIALS AND METHODS

Study design

A retrospective case review of 22 non-HIV-infected PJP patients admitted to Dongyang Hospital Affiliated to Wenzhou Medical University, a tertiary hospital in Zhejiang, China was carried out between October 2019 and April 2021. Patient data including symptoms, laboratory results, dynamic and comprehensive computed tomography data, and clinical course of the disease were extracted from electronic medical records. Information on treatment, response to treatment, outcomes, and any follow-up data were also collected. The study protocol was approved by the Ethics Committee of the Dongyang Hospital Affiliated to Wenzhou Medical University, (No. 2021-YX-127). All data were anonymized prior to analysis.

RESULTS

Patient characteristics

In total, four women and 18 men diagnosed as non-HIV-infected PJP were enrolled in the study. The median age of these patients was 61.18 ± 16.51 (range 17–84) years (Table 1). All patients tested positive for *Pneumocystis jirovecii* DNA fragments as determined using metagenomic next-generation sequencing (mNGS). Systematic screening did not identify any other respiratory pathogens at the time of hospital admission. All patients presented with dry cough and dyspnea, whereas 13 patients had fever. The median time from onset of illness to admission was 5.68 ± 3.66 (range 1–15) d. On physical examination, the patients presented with heterogeneous and nonspecific clinical signs. Among the comorbidities found were autoimmune disease ($n = 5$), non-Hodgkin's lymphoma ($n = 4$), lung cancer ($n = 7$; all underwent chest radiotherapy), organ transplantation ($n = 2$), and membranous nephropathy ($n = 4$). All patients developed respiratory failure and received oxygen therapy (oxygen therapy, administered nasally for 11 patients, mask oxygen therapy for 10 patients, and high flow nasal cannula therapy for 1 patient). No patient received invasive mechanical ventilation.

Technical investigations

Clinical examination carried out at admission showed that patients had a mean white blood cell count of $9.69 \pm 6.22 \times 10^9/L$ and with a proportion of neutrophils of $0.82 \pm 0.14\%$. In addition, C-reactive protein level was 79.69 ± 64.21 mg/L, lactate dehydrogenase (LDH) level was 408.23 ± 117.87 U/L, and procalcitonin level was 0.23 ± 0.21 ng/mL.

Lung imaging revealed lesions in the upper lobe of lung in the early stage. With progression of the disease, the lesions spread to the lower lobe of the lung. The most common imaging manifestation was widespread ground glass opacity, which had a mosaic or diffuses distribution, mainly in the upper lobe of the lung (Figures 1 and 2).

Treatment

Analysis of medical records showed that most of the patients were treated with antibiotics such as cephalosporin prior to admission. However, their symptoms gradually deteriorated leading to development of progressive dyspnea. After hospital admission, patients underwent bronchofibroscopy and alveolar lavage fluid was collected for mNGS analysis.

mNGS analysis was carried out within 48–72 h from the time of sample collection to the time results were reported. After confirmation of PJP, treatment was changed to TMP-SMX (TMP, 15–20 mg/kg/d; SMX, 75–100 mg/kg/d), administered for at least 2 wk, as reported previously[8]. Patients received TMP-SMX combined with caspofungin (through intravenous administration of 70 mg QD on the first day and 50 mg QD as the maintenance dose afterwards) for those with respiratory failure or renal insufficiency. In addition, moderate to severe non-HIV-infected PJP patients received glucocorticoid treatment ($n = 17$) for 1 wk.

Outcomes

After initiation of therapy, the body temperature gradually returned to normal within 3 d, and their respiratory function improved. Further analysis revealed that the level of inflammatory indices in blood significantly decreased, and the lung lesions gradually disappeared following treatment. All patients had fully recovered before discharge.

DISCUSSION

The incidence of PJP is high among immunocompromised HIV-negative patients. This calls for development of novel diagnostic, treatment, and prevention strategies for non-HIV-infected PJP[9–11]. Non-HIV-infected PJP patients have an acute onset, rapid disease progression, poor prognosis, and higher mortality rates compared with HIV-infected PJP patients[12–16].

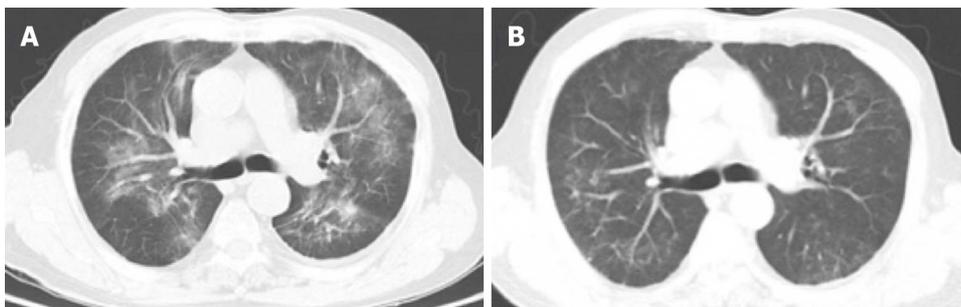
The population of HIV-negative patients susceptible to *Pneumocystis jirovecii* includes patients who have undergone transplantation, hemato-oncological patients, and those taking immunosuppressive drugs for autoimmune diseases. Approximately 20% of non-HIV-infected PJP patients are those with autoimmune diseases, mainly nodular polyarteritis, granuloma with polyarteritis, dermatomyositis/polymyositis, and rheumatoid arthritis with interstitial pneumonia[17,18]. So far, several drugs such as, long-term use of medium and high-dose glucocorticoids, cyclophosphamide, rituximab, alemtuzumab (a monoclonal antibody used for treatment of chronic B-cell lymphoblastic leukemia and multiple sclerosis), and tumor necrosis factor α antagonists have been linked to the occurrence of PJP[19, 20].

The main symptoms of non-HIV-infected PJP patients include fever, dyspnea and dry cough. Moreover, hypoxia and respiratory failure are more common in non-HIV-infected PJP patients compared with HIV-infected PJP patients. However, frequency of LDH elevation is lower, the onset and disease progression are more rapid (often within a few days) in non-HIV-infected PJP than in HIV-

Table 1 Clinical characteristics of *Pneumocystis jirovecii* pneumonia cases

Characteristics	Patients, n (%)	Median value (range)
Demographics		
Male/female	18/4	
Age, median (range, yr)		61.18 ± 16.51
Underlying disease	22/22	
Clinical manifestations		
Fever	13/22	
Cough	22/22	
Dyspnea	22/22	
Laboratory tests		
WBC (normal 4×10^9 – 10×10^9 /L)		9.69 ± 6.22
Percentage of neutrophils		0.82 ± 0.14
CRP (normal 0–8 mg/L)		79.69 ± 64.21
PCT (normal 0–0.5 ng/mL)		0.23 ± 0.21
LDH (normal 120–250 U/L)		408.23 ± 117.87
Oxygenation index		209.55 ± 35.03
CD4+ T lymphocyte counts		0.81 ± 0.52
Imaging		
Diffuse ground glass opacity	19/22 (86.36%)	
Streak like dense shadow	3/22 (13.64%)	
Complete CT recovery in survivors	22/22 (100.0%)	

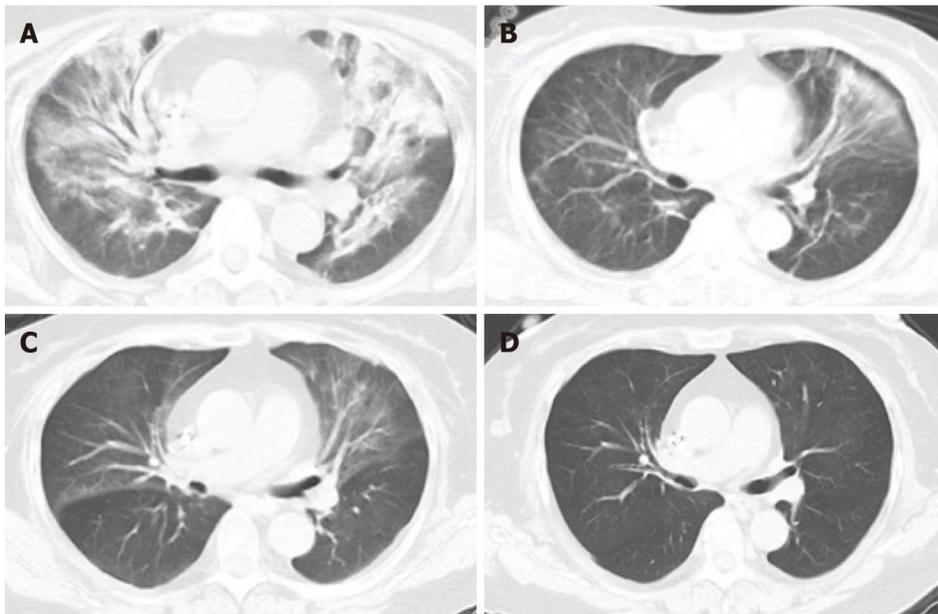
CRP: C-reactive protein; CT: Computed tomography; PCT: Procalcitonin; WBC: White blood cell; LDH: Lactate dehydrogenase.



DOI: 10.12998/wjcc.v10.i9.2743 Copyright ©The Author(s) 2022.

Figure 1 A 76-year-old man with rheumatic polymyalgia who under 8 mg/wk methotrexate treatment attended our hospital with complaints of cough and fever. A: The patient presented with respiratory failure and received 3 L/min oxygen therapy nasally. Computed tomography (CT) indicated bilateral infiltration dominantly in the hilum. The patient received bronchoscopy the day after admission. Next-generation sequencing analysis of the bronchoalveolar lavage fluid was positive for *Pneumocystis jirovecii*. The patient was diagnosed with severe non-human immunodeficiency virus-infected *Pneumocystis jirovecii* pneumonia. Daily oral administration of 12 mg/kg trimethoprim (TMP) and 60 mg/kg sulfamethoxazole (SMX) [oral administration of two tablets of TMP (80 mg) and SMX (400 mg), four times daily] and caspofungin (intravenous administration of 70 mg QD for the first day and 50 mg QD for maintenance) was initiated and continued for 14 d without any adverse events; B: The respiratory status of the patient improved gradually. CT at 14 d after start of treatment showed restoration of respiration. The patient was discharged on day 18 of hospitalization.

infected PJP. For non-HIV-infected PJP patients, physical examination is nonspecific, and lung auscultation is usually normal, but often inconsistent for those with severe clinical manifestations[21]. Computed tomography (CT) scans show ground-glass opacity (GGO), mainly presenting with a central distribution, is a common radiological pattern for PJP patients. These manifestations were observed in patients included in the current study (Figure 1). GGOs may present as a mosaic-like distribution or



DOI: 10.12998/wjcc.v10.i9.2743 Copyright ©The Author(s) 2022.

Figure 2 A 62-year-old woman with membranous nephropathy who was undergoing treatment with 15 mg/d methylprednisolone was admitted to our hospital with complaints of cough and dyspnea. A: The patient presented with respiratory failure and received 5 L/min mask oxygen therapy. Computed tomography (CT) showed bilateral infiltration dominantly in the hilum. The patient received bronchoscopy 1 d after admission. Next-generation sequencing of using bronchoalveolar lavage fluid sample was positive for *Pneumocystis jirovecii*, thus the patient was diagnosed with severe non-human immunodeficiency virus-infected *Pneumocystis jirovecii* pneumonia. Daily oral administration of trimethoprim-sulfamethoxazole (TMP-SMX) [oral administration of two tablets of TMP (80 mg) and SMX (400 mg), twice daily, adjusted based on renal function] and caspofungin (intravenous administration of 70 mg QD for the first day and 50 mg QD for maintenance) was initiated and continued for 14 d without any adverse events; B-D: The respiratory status of the patient improved gradually, and CT showed that respiratory function was restored at the last day of treatment.

diffuse distribution, more commonly occurring in the upper lobes of the lungs[22]. In the advanced stages of the disease, CT scans show lung consolidation. Paving stone-like manifestations are observed in 6%–18% of patients[23]. Hollowness and pleural effusion are rare, and if they occur, they often indicate existence of other diseases[23]. Approximately 3%–6% of non-HIV-infected PJP patients may present with lung cyst-like changes of different shapes, sizes, and wall thicknesses, implying that they are susceptible to spontaneous pneumothorax[23]. GGOs in non-HIV-infected PJP patients spread faster compared than in HIV-infected PJP patients.

Pneumocystis jirovecii cannot be cultured in the laboratory. Therefore, this infection has been traditionally diagnosed based on microscopic observation of the organisms in respiratory specimens. However, due to the lower pathogen burden in non-HIV-infected PJP patients compared with HIV-infected PJP patients, specimens from non-HIV-infected PJP patients have lower microscopic sensitivity [24,25]. A combination of different diagnostic methods, such as microscopy, polymerase chain reaction, and (1,3)- β -D-glucan detection have been previously adopted to increase the diagnosis rate. Silver staining can detect cysts with high specificity. However, the sensitivity of this method is not satisfactory. PJP patients have a higher number of trophozoites than cysts, thus Giemsa and Diff-Quik stains used for the detection of trophozoites should have high sensitivity. Moreover, the results depend on the skill and experience of the examiner. Advances in technology have led to development of mNGS which can unbiasedly detect various pathogenic microorganisms in clinical samples. This approach ensures rapid screening of pathogens, and provides timely identification of pathogens. Therefore, it is currently applied in the detection of pathogens that cause infectious diseases. Bronchoalveolar lavage fluid (BALF) is the preferred specimen, as BALF provides a higher diagnosis rate, and can be used to identify other pathogens, such as tuberculosis, histoplasmosis and cytomegalovirus infection. Induced sputum testing can be used as an alternative method if the patient cannot tolerate bronchoscopy, however, its diagnostic sensitivity is lower compared to that of BALF (55%–90%)[26,27].

Current guidelines and published reviews state that the first-line treatment for non-HIV-infected PJP is TMP-SMX[7,8,28]. However, prolonged use of TMP-SMX may increase risk of drug resistance and side effects. Some patients cannot tolerate high doses of this treatment however, low-dose therapy is well-tolerated and has fewer side effects[29]. In the current study, one patient developed renal impairment during treatment, but renal function was restored when the dosage was reduced. Therefore, the dose of TMP-SMX should be adjusted based on the renal function of the patient. If the patient is taking immunosuppressants during treatment, the dose of immunosuppressants should be reduced, suspended, or stopped. However, the dose should be individualized. Previous studies have shown that caspofungin alone or in combination with TMP-SMX is effective for HIV-infected PJP patients, and

casprofungin can also be used as a remedial drug[30,31]. In the current study, all patients were successfully treated with casprofungin combined with TMP-SMX. This finding indicates that casprofungin can cure PJP; however, these findings should be validated in large-sample clinical studies. According to current guidelines, standard treatment should be used for 2–3 wk[8]. The duration should be appropriately extended until respiratory function is stable for non-HIV-infected PJP patients with severe immunosuppression, high pneumocystis load, and slow clinical improvement[8,28]. Non-HIV-infected PJP patients present with severe inflammation and some studies recommend use of adjuvant glucocorticoid to control it[31]. In the current study, 17 patients underwent adjuvant treatment of glucocorticoids for 7 d with good results. This indicates that patients with moderate to severe disease should be put under adjunctive corticosteroids to improve survival.

CONCLUSION

Non-HIV-infected PJP patients manifest with rapid disease progression, respiratory failure, and high mortality. Physicians should be aware that PJP is an important infectious complication in hematological and post-transplant patients, including who undergo solid organ transplant, allogenic or autologous hematopoietic stem cell transplantation. It is also common in patients taking immunosuppressive drugs. For non-HIV-infected PJP patients with respiratory failure, or patients with renal insufficiency, TMP-SMX combined with casprofungin can alleviate symptoms and accelerate recovery. Several challenges are encountered in the treatment of non-HIV-infected PJP patients, such as difficulty of determining the timing and duration of adjunctive treatment using glucocorticoids and identification of patients susceptible to *pneumocystis jirovecii* infection. Therefore, future studies should explore methods to circumvent these challenges.

ARTICLE HIGHLIGHTS

Research background

Incidence of non-human immunodeficiency virus (HIV)-infected *Pneumocystis jirovecii* pneumonia (PJP) patients has been increasing annually owing to increased use of immunosuppressants and organ transplantation. In addition, management of non-HIV-infected PJP patients is not standardized as it is the case for HIV-infected PJP patients, and the clinical attention is poor compared with that of HIV-infected PJP patients.

Research motivation

The aim of this retrospective study was to explore the characteristics of non-HIV-infected PJP treated with trimethoprim-sulfamethoxazole (TMP-SMX) and casprofungin.

Research objectives

The findings of the current study will improve understanding of PJP in non-HIV-infected patients, and reduce misdiagnosis rate and mortality rate of non-HIV-infected PJP patients.

Research methods

A retrospective case review of 22 non-HIV-infected PJP patients admitted to Dongyang Hospital Affiliated to Wenzhou Medical University was conducted between October 2019 and April 2021. Patient data on symptoms, laboratory results, dynamic and comprehensive computed tomography, and clinical course of the disease were extracted from electronic medical records. Additional data on treatment, response to treatment, outcomes, and any relevant follow-up data were also collected.

Research results

A total of 22 cases of non-HIV-infected PJP were included in the current study. Clinical manifestations of patients mainly included fever, dry cough, and progressive dyspnea. All patients presented with an acute onset and respiratory failure. The most common imaging manifestation was ground glass opacity around the hilar, mainly located in the upper lobe. All patients underwent diagnosis using next-generation sequencing, and were all treated with TMP-SMX and casprofungin. Seventeen patients received short-term adjuvant glucocorticoid therapy. All patients recovered and were discharged from hospital.

Research conclusions

Non-HIV-infected PJP patients are characterized by rapid disease progression, high risk of respiratory failure, and high mortality. The findings of the current study showed that a combination of TMP-SMX and casprofungin is an effective treatment option for severe non-HIV-infected PJP patients with

respiratory failure.

Research perspectives

The timing and duration of adjunctive treatment using glucocorticoids and identification of patients susceptible to *Pneumocystis jirovecii* infection at an early stage to start effective prophylaxis drugs.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design; Material preparation and data analysis were performed by Feng LF and Chen YX; The first draft of the manuscript was written by Wu HH; Fang SY re-evaluated and added content on the computed tomography imaging outcomes; All authors were involved in the review of various previous versions of the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: The study protocol was approved by the Ethics Committee of the Dongyang Hospital Affiliated to Wenzhou Medical University (No. 2021-YX-127).

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: All data generated or analyzed during this study are included in this published article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Huan-Huan Wu 0000-0001-8324-9570; Shuang-Yan Fang 0000-0001-8713-1342; Yan-Xiao Chen 0000-0002-0428-6507; Lan-Fang Feng 0000-0001-7626-9389.

S-Editor: Zhang H

L-Editor: Kerr C

P-Editor: Zhang H

REFERENCES

- 1 **Fauci AS**, Macher AM, Longo DL, Lane HC, Rook AH, Masur H, Gelmann EP. NIH conference. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984; **100**: 92-106 [PMID: 6318629 DOI: 10.7326/0003-4819-100-1-92]
- 2 **Masur H**, Ognibene FP, Yarchoan R, Shelhamer JH, Baird BF, Travis W, Suffredini AF, Deyton L, Kovacs JA, Falloon J. CD4 counts as predictors of opportunistic pneumonias in human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1989; **111**: 223-231 [PMID: 2546472 DOI: 10.7326/0003-4819-111-3-223]
- 3 Recommendations for prophylaxis against *Pneumocystis carinii* pneumonia for adults and adolescents infected with human immunodeficiency virus. *MMWR Recomm Rep* 1992; **41**: 1-11 [PMID: 1348843]
- 4 **Kovacs JA**, Ng VL, Masur H, Leoung G, Hadley WK, Evans G, Lane HC, Ognibene FP, Shelhamer J, Parrillo JE. Diagnosis of *Pneumocystis carinii* pneumonia: improved detection in sputum with use of monoclonal antibodies. *N Engl J Med* 1988; **318**: 589-593 [PMID: 2449613 DOI: 10.1056/NEJM198803103181001]
- 5 **Varthalitis I**, Aoun M, Daneau D, Meunier F. *Pneumocystis carinii* pneumonia in patients with cancer. An increasing incidence. *Cancer* 1993; **71**: 481-485 [PMID: 8422642 DOI: 10.1002/1097-0142(19930115)71:2<481::aid-cnrcr2820710232>3.0.co;2-s]
- 6 **Arend SM**, Kroon FP, van't Wout JW. *Pneumocystis carinii* pneumonia in patients without AIDS, 1980 through 1993. An analysis of 78 cases. *Arch Intern Med* 1995; **155**: 2436-2441 [PMID: 7503602]
- 7 **van Well G**, van Furth M. *Pneumocystis pneumonia*. *N Engl J Med* 2004; **351**: 1262-1263 [PMID: 15376355]
- 8 **Limper AH**, Knox KS, Sarosi GA, Ampel NM, Bennett JE, Catanzaro A, Davies SF, Dismukes WE, Hage CA, Marr KA, Mody CH, Perfect JR, Stevens DA; American Thoracic Society Fungal Working Group. An official American Thoracic Society statement: Treatment of fungal infections in adult pulmonary and critical care patients. *Am J Respir Crit Care Med* 2011; **183**: 96-128 [PMID: 21193785 DOI: 10.1164/rccm.2008-740ST]
- 9 **McKinnell JA**, Cannella AP, Kunz DF, Hook EW 3rd, Moser SA, Miller LG, Baddley JW, Pappas PG. *Pneumocystis pneumonia* in hospitalized patients: a detailed examination of symptoms, management, and outcomes in human immunodeficiency virus (HIV)-infected and HIV-uninfected persons. *Transpl Infect Dis* 2012; **14**: 510-518. [PMID: 22548840 DOI: 10.1111/j.1399-3062.2012.00739.x]
- 10 **Bienvenu AL**, Traore K, Plekhanova I, Bouchrik M, Bossard C, Picot S. *Pneumocystis pneumonia* suspected cases in 604 non-HIV and HIV patients. *Int J Infect Dis* 2016; **46**: 11-17 [PMID: 27021532 DOI: 10.1016/j.ijid.2016.03.018]

- 11 **Avino LJ**, Naylor SM, Roecker AM. Pneumocystis jirovecii Pneumonia in the Non-HIV-Infected Population. *Ann Pharmacother* 2016; **50**: 673-679 [PMID: [27242349](#) DOI: [10.1177/1060028016650107](#)]
- 12 **Roux A**, Canet E, Valade S, Gangneux-Robert F, Hamane S, Lafabrie A, Maubon D, Debourgogne A, Le Gal S, Dalle F, Letierrier M, Toubas D, Pomares C, Bellanger AP, Bonhomme J, Berry A, Durand-Joly I, Magne D, Pons D, Hennequin C, Maury E, Roux P, Azoulay É. Pneumocystis jirovecii pneumonia in patients with or without AIDS, France. *Emerg Infect Dis* 2014; **20**: 1490-1497 [PMID: [25148074](#) DOI: [10.3201/eid2009.131668](#)]
- 13 **Reid AB**, Chen SC, Worth LJ. Pneumocystis jirovecii pneumonia in non-HIV-infected patients: new risks and diagnostic tools. *Curr Opin Infect Dis* 2011; **24**: 534-544 [PMID: [21986616](#) DOI: [10.1097/QCO.0b013e32834cac17](#)]
- 14 **Matsumura Y**, Shindo Y, Iinuma Y, Yamamoto M, Shirano M, Matsushima A, Nagao M, Ito Y, Takakura S, Hasegawa Y, Ichiyama S. Clinical characteristics of Pneumocystis pneumonia in non-HIV patients and prognostic factors including microbiological genotypes. *BMC Infect Dis* 2011; **11**: 76 [PMID: [21439061](#) DOI: [10.1186/1471-2334-11-76](#)]
- 15 **Li MC**, Lee NY, Lee CC, Lee HC, Chang CM, Ko WC. Pneumocystis jirovecii pneumonia in immunocompromised patients: delayed diagnosis and poor outcomes in non-HIV-infected individuals. *J Microbiol Immunol Infect* 2014; **47**: 42-47 [PMID: [23063081](#) DOI: [10.1016/j.jmii.2012.08.024](#)]
- 16 **Yu Q**, Jia P, Su L, Zhao H, Que C. Outcomes and prognostic factors of non-HIV patients with pneumocystis jirovecii pneumonia and pulmonary CMV co-infection: A Retrospective Cohort Study. *BMC Infect Dis* 2017; **17**: 392 [PMID: [28583135](#) DOI: [10.1186/s12879-017-2492-8](#)]
- 17 **Harigai M**, Koike R, Miyasaka N; Pneumocystis Pneumonia under Anti-Tumor Necrosis Factor Therapy (PAT) Study Group. Pneumocystis pneumonia associated with infliximab in Japan. *N Engl J Med* 2007; **357**: 1874-1876 [PMID: [17978303](#) DOI: [10.1056/NEJMc070728](#)]
- 18 **Yates M**, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, Hellmich B, Holle JU, Laudien M, Little MA, Luqmani RA, Mahr A, Merkel PA, Mills J, Mooney J, Segelmark M, Tesar V, Westman K, Vaglio A, Yalçındağ N, Jayne DR, Mukhtyar C. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016; **75**: 1583-1594 [PMID: [27338776](#) DOI: [10.1136/annrheumdis-2016-209133](#)]
- 19 **Martin-Garrido I**, Carmona EM, Specks U, Limper AH. Pneumocystis pneumonia in patients treated with rituximab. *Chest* 2013; **144**: 258-265 [PMID: [23258406](#) DOI: [10.1378/chest.12-0477](#)]
- 20 **Grubbs JA**, Baddley JW. Pneumocystis jirovecii pneumonia in patients receiving tumor-necrosis-factor-inhibitor therapy: implications for chemoprophylaxis. *Curr Rheumatol Rep* 2014; **16**: 445 [PMID: [25182673](#) DOI: [10.1007/s11926-014-0445-4](#)]
- 21 **Thomas CF Jr**, Limper AH. Pneumocystis pneumonia. *N Engl J Med* 2004; **350**: 2487-2498 [PMID: [15190141](#) DOI: [10.1056/NEJMra032588](#)]
- 22 **Kovacs JA**, Hiemenz JW, Macher AM, Stover D, Murray HW, Shelhamer J, Lane HC, Urmacher C, Honig C, Longo DL. Pneumocystis carinii pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med* 1984; **100**: 663-671 [PMID: [6231873](#) DOI: [10.7326/0003-4819-100-5-663](#)]
- 23 **Vogel MN**, Vatlach M, Weissgerber P, Goepfert B, Claussen CD, Hetzel J, Horgor M. HRCT-features of Pneumocystis jirovecii pneumonia and their evolution before and after treatment in non-HIV immunocompromised patients. *Eur J Radiol* 2012; **81**: 1315-1320 [PMID: [21420818](#) DOI: [10.1016/j.ejrad.2011.02.052](#)]
- 24 **Alanio A**, Hauser PM, Lagrou K, Melchers WJ, Helweg-Larsen J, Matos O, Cesaro S, Maschmeyer G, Einsele H, Donnelly JP, Cordonnier C, Maertens J, Bretagne S; 5th European Conference on Infections in Leukemia (ECIL-5), a joint venture of The European Group for Blood and Marrow Transplantation (EBMT), The European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and The European LeukemiaNet (ELN). ECIL guidelines for the diagnosis of Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother* 2016; **71**: 2386-2396 [PMID: [27550991](#) DOI: [10.1093/jac/dkw156](#)]
- 25 **Alanio A**, Desoubreux G, Sarfati C, Hamane S, Bergeron A, Azoulay E, Molina JM, Derouin F, Menotti J. Real-time PCR assay-based strategy for differentiation between active Pneumocystis jirovecii pneumonia and colonization in immunocompromised patients. *Clin Microbiol Infect* 2011; **17**: 1531-1537 [PMID: [20946413](#) DOI: [10.1111/j.1469-0691.2010.03400.x](#)]
- 26 **Limper AH**, Offord KP, Smith TF, Martin WJ 2nd. Pneumocystis carinii pneumonia. Differences in lung parasite number and inflammation in patients with and without AIDS. *Am Rev Respir Dis* 1989; **140**: 1204-1209 [PMID: [2817582](#) DOI: [10.1164/ajrccm/140.5.1204](#)]
- 27 **Pagano L**, Fianchi L, Mele L, Girmenia C, Offidani M, Ricci P, Mitra ME, Picardi M, Caramatti C, Piccaluga P, Nosari A, Buelli M, Allione B, Cortelezzi A, Fabbiano F, Milone G, Invernizzi R, Martino B, Masini L, Todeschini G, Cappucci MA, Russo D, Corvatta L, Martino P, Del Favero A. Pneumocystis carinii pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres. *Br J Haematol* 2002; **117**: 379-386 [PMID: [11972521](#) DOI: [10.1046/j.1365-2141.2002.03419.x](#)]
- 28 **Tasaka S**, Tokuda H. Pneumocystis jirovecii pneumonia in non-HIV-infected patients in the era of novel immunosuppressive therapies. *J Infect Chemother* 2012; **18**: 793-806 [PMID: [22864454](#) DOI: [10.1007/s10156-012-0453-0](#)]
- 29 **Nakashima K**, Aoshima M, Nakashita T, Hara M, Otsuki A, Noma S, Misawa M, Otsuka Y, Motojima S. Low-dose trimethoprim-sulfamethoxazole treatment for pneumocystis pneumonia in non-human immunodeficiency virus-infected immunocompromised patients: A single-center retrospective observational cohort study. *J Microbiol Immunol Infect* 2018; **51**: 810-820 [PMID: [28779879](#) DOI: [10.1016/j.jmii.2017.07.007](#)]
- 30 **Mu XD**, Que CL, He B, Wang GF, Li HC. Caspofungin in salvage treatment of severe pneumocystis pneumonia: case report and literature review. *Chin Med J (Engl)* 2009; **122**: 996-999 [PMID: [19493430](#)]
- 31 **Hof H**, Schnülle P. Pneumocystis jirovecii pneumonia in a patient with Wegener's granulomatosis treated efficiently with caspofungin. *Mycoses* 2008; **51**: 65-67 [PMID: [18471163](#) DOI: [10.1111/j.1439-0507.2008.01530.x](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

