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Carrimycin in the treatment of acute promyelocytic leukemia combined with pulmonary tuberculosis: A case report

Yang FY *et al.* Carrimycin, APL and PTB treatment

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Abstract

BACKGROUND

Pulmonary tuberculosis (PTB) is prevalent in immunocompromised populations, including patients with hematologic malignancies, human immunodeficiency virus infections, and chronic diseases. Effective treatment for acute promyelocytic leukemia (APL) combined with PTB is lacking. These patients show an extremely poor prognosis. Therefore, studies should establish efficient treatment options to improve patient survival and prognosis.

CASE SUMMARY

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A 60-year-old male with pain in the right side of his chest and a fever for 4 d visited the outpatient department of our hospital. Peripheral blood smear revealed 54% blasts. Following bone marrow examinations, variant APL with TNRC18-RARA fusion gene was diagnosed. Chest computed tomography scan showed bilateral pneumonitis with bilateral pleural effusions, partial atelectasis in the lower lobes of both lungs, and the bronchoalveolar lavage fluid gene X-Pert test was positive, indicative of PTB. Carrimycin, ethambutol (EMB), and isoniazid (INH) were administered since he could not receive chemotherapy as the WBC count decreased continuously. After one week of treatment

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with carrimycin, the patient recovered from fever and received chemotherapy. Chemotherapy was very effective and his white blood cells counts got back to normal. After being given five months with rifampin, EMB and INH and chemotherapy, the patient showed complete remission from pneumonia and APL.

CONCLUSION

We report a case of PTB treated successfully with carrimycin with APL that requires chemotherapy.

Key Words: Carrimycin; Hematologic disease; Acute myeloid leukemia; Acute promyelocytic leukemia; Pulmonary tuberculosis; Case report

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Core Tip: Here, we report a case of a patient with acute promyelocytic leukemia (APL) combined with pulmonary tuberculosis (PTB). Addition of carrimycin in a patient with tuberculosis in remission thus enabling chemotherapy for leukemia. He could not tolerate the side effects of routine anti-tuberculosis drugs because of a low white blood cell count, so carrimycin was used for treatment for PTB. He achieved complete remission of APL and PTB after six months treatment. Further research is necessary to determine whether carrimycin is therapeutically useful in PTB.

INTRODUCTION

⁸ A subtype of acute myeloid leukemia (AML) is acute promyelocytic leukemia (APL). A heterogeneous disease of hematological malignancies known as AML is characterized by aberrant clonal proliferation, poor differentiation, and inhibition of myeloid hematopoietic stem cell apoptosis^[1]. Patients with AML have qualitative and quantitative deficits in granulocytes that predispose them to bacterial and fungal infections. Chemotherapeutic regimens often complicate these deficits, resulting in prolonged periods of severe neutropenia and disruption of mucosal barriers, further elevating the risk of infection^[2]. Patients with hematological malignancies have a higher risk of developing PTB^[3]. However, anti-tuberculosis chemotherapy is limited by adverse side effects and limited drug options. Few studies have investigated the treatment options for APL in combination with PTB. ¹ Here, we report a case of PTB in a patient with APL who achieved considerable relief from after carrimycin treatment. ¹⁰ This case report provides evidence for the use of carrimycin as a therapeutic approach for PTB with APL and offers a clinical direction for treating PTB.

² CASE PRESENTATION

Chief complaints

A 60-year-old male presented with pain in his right chest and a fever for the last 4 d. ²

History of present illness

The patient presented with dull pain in the right chest aggravated by deep breathing and activity. His highest recorded temperature was 38.6 °C, accompanied by generalized fatigue, muscle and joint pain, and occasional coughing with a small amount of white sputum. The patient was treated at home with self-administered antipyretic drugs after disease onset, with poor results. Before admission, the patient visited a local hospital where examinations revealed pancytopenia, pneumonia, and pleural effusion.

² *History of past illness*

The patient had a history of hypertension for more than 10 years, which was well controlled with valsartan and amlodipine.

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Personal and family history

The patient had a history of smoking for more than 30 years (60 cigarettes per day) and drinking for more than 20 years (200 g of liquor per day). The patient's father had died of esophageal cancer.

Physical examination

Physical symptoms were as follows: temperature, 36.8 °C; blood pressure, 132/75 mmHg; heart rate, 78 beats per min, and respiratory rate, 19 breaths per min. Physical examination revealed no palpable enlargement of the superficial lymph nodes throughout the body, no moist rales in either lungs, or hepatosplenomegaly.

Laboratory examinations

Pancytopenia (absolute monocyte count: $3.55 \times 10^9/L$; percentage monocyte: 53.30%; absolute neutrophil count: $1.85 \times 10^9/L$; hemoglobin: 76 g/L; platelet: $101 \times 10^9/L$) was identified during the initial examination. Peripheral blood smear revealed 54% blasts. C-reactive protein (190.39 mg/L), and D-dimer (29.64 mg/L) levels were increased. Bone marrow smear suggested a high probability of APL. Reggie's stain showed promyelocyte accounted for about 55% and Peroxidase stain was positivity (Figure 1A and B). A bone marrow biopsy was subsequently performed which revealed a small number of cells with moderately enlarged cytosomes, deviated nuclei, fine chromatin, and inconspicuous nucleoli, requiring clinical and other tests to exclude AML. Flow cytometry of the specimens was consistent with the immunophenotype of AML. Leukemia-associated 45 fusion genes were not detected. Chromosomal karyotype analysis revealed the presence of 46, XY, i(7)(q10), inc(4)/46, XY(6). Fluorescence in situ hybridization confirmed the rearrangement of RARA. Hematology-associated fusion genes were identified, and the TNRC18-RARA fusion gene was detected. The patient underwent repeated

bronchoscopies and the final bronchoalveolar lavage fluid (BALF) gene X-Pert test was positive.

Imaging examinations

Chest computed tomography scans revealed bilateral pneumonitis with ⁵pleural effusion, partial atelectasis in the lower lobes of both lungs (Figure 2A). The patient's lung inflammation gradually deteriorated (Figure 2B). Multiple bronchoscopies were performed, and the BALF gene X-Pert test was positive.

FINAL DIAGNOSIS

The patient was finally diagnosed with APL combined with PTB.

TREATMENT

Initially, the patient received treatment with ceftriaxone sodium, piperacillin-tazobactam, cefoperazone sodium, sulbactam sodium, meropenem, voriconazole, posaconazole, linezolid (LZD), caspofungin, and amphotericin B cholesteryl sulfate complex, which was ineffective, and he continued to experience fever recurrently (Figure 2A-C). During this period, the patient received three courses of chemotherapy for APL. After PTB diagnosis, he was administered ¹⁸rifampicin (0.45 g, qd), ¹²isoniazid (INH; 0.3 g, qd) and ethambutol (EMB; 0.75 g, qd) as anti-tuberculosis chemotherapy. Unfortunately, the patient's WBC count continued to decrease, making it impossible for the patient to continue anti-tuberculosis chemotherapy. Chemotherapy could not be administered for leukemia because PTB was not controlled, leading to recurrent fever. Therefore, carrimycin (0.4 g, qd) was administered to the patient for 24 d. His lung infection improved significantly. ⁷Rifampicin (0.45 g, qd), INH (0.3 g, qd) and EMB (0.75 g, qd) were administered as anti-tuberculosis treatment for six months. The fourth cycle of venetoclax (200 ¹³mg on days 1–4, 400 mg on days 5–14) and azacitidine (100 mg on days 1–7) combination treatment for leukemia was initiated when the patient's white blood cell (WBC) count returned to the normal range. Reggie's stain twice showed that the patient achieved clinical complete

response after chemotherapy (Figure 1C and D). PTB and APL showed complete remission after six months of treatment (Figure 2D and E). The changes of the patient's WBC count during treatment are shown in Figure 3.

OUTCOME AND FOLLOW-UP

Carrimycin (0.4 g, qd) was administered for 24 d, and the lung infection improved dramatically. Chemotherapy for leukemia can be administered normally. The patient achieved complete remission after six months of treatment.

DISCUSSION

APL is a highly heterogeneous disease caused by the aberrant differentiation of myeloid lineage cells in the hematopoietic system^[4]. Patients with APL have reduced autoimmune function and are susceptible to co-infections. The risk of developing tuberculosis is higher in patients with hematological malignancies. A direct result of immunosuppression brought on by the malignancy, a side effect of treatment, or a combination of both can increase susceptibility to PTB^[5]. Herein, we report a case of APL combined with PTB. X-Pert is a rapid nucleic acid amplification test used to tuberculosis^[6]. The patient's BALF gene X-Pert test result was positive, confirming the diagnosis of tuberculosis. After a definitive diagnosis, the patient received both anti-tuberculosis and leukemia chemotherapy. However, anti-tuberculosis chemotherapy resulted in a persistent decrease in WBC count and was subsequently discontinued, causing recurrent fever, which made it impossible to properly administer leukemia chemotherapy. The patient was treated with carrimycin, INH, and EMB to control the lung infections so that leukemia chemotherapy could be administered. Surprisingly, the patient had no fever on the day carrimycin was added. The patient's WBC count normalized after five days of treatment, and the fourth cycle of leukemia chemotherapy with venetoclax combined with azacytidine was subsequently initiated. The patient achieved complete remission after six months of treatment.

APL and PTB have seldom been documented. Abdullah *et al*^[7] described a case of APL combined with tuberculosis in a patient receiving the PETHEMA protocol consisting of ATRA plus Idarubicin and anti-TB treatment. Due to the interaction of several anti-tuberculosis drugs with chemotherapy, treating tuberculosis in patients with acute leukemia can be challenging. Susan Realegeno *et al.* reported a case of a patient with APL developing disseminated tuberculosis while undergoing APL therapy. The patient was treated with rifampin (RIF), pyrazinamide (PZA), moxifloxacin (MFX), and EMB, INH, levofloxacin, amikacin and LZD as anti-tuberculosis therapy^[8]. Conventional chemotherapy regimens for leukemia are myelosuppressive, making them ineffective for active PTB control^[5]. Recurrent fever due to uncontrolled tuberculosis can limit the use of chemotherapeutic regimens for leukemia. RIF, INH, PZA, and EMB are well-known first-line medications. The selection of anti-tuberculosis drugs is limited owing to factors such as multidrug resistance and adverse effects of the drugs^[9]. In our patient, carrimycin was added because of a persistent decrease in WBC count after the application of conventional anti-tuberculosis chemotherapy, which showed promising results for anti-tuberculosis treatment. Azacitidine has the potential to cause reactivation of tuberculosis^[5].

Carrimycin is a new national class I drug that has been approved by the CFDA for treating acute tracheal bronchitis caused by *Haemophilus influenzae* and *Streptococcus pneumoniae* and acute sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Moraxella catarrhalis*, and *Staphylococcus*^[10]. Carrimycin exerts an inhibitory effect on inflammation^[11]. Carrimycin considerably decreases interleukin (IL)-4 levels in the lungs and kidneys, especially in the liver and spleen. Furthermore, carrimycin significantly decreases IL-1 β levels in the spleen, liver, and kidneys, especially in the small intestine and the lungs, showing an excellent anti-inflammatory effect^[11]. Second, carrimycin is a novel macrolide antibiotic with excellent antibacterial effects that can inhibit bacterial protein synthesis by blocking the activity of peptidyl transferase in the 50s ribosome subunit to develop antibacterial effects^[11]. Carrimycin has significant efficacy against multidrug-resistant bacteria that do not respond to conventional anti-

infective treatment^[12]. Carrimycin is a dual-acting immunoantibiotic with antibacterial and immunomodulatory properties. In terms of intrinsic immunity, carrimycin promotes neutrophil migration to the sites of inflammation and enhances phagocytosis by macrophages. In terms of adaptive immunity, carrimycin significantly increased the total T-cell population (CD3-positive cells), along with an increase in both CD4- and CD8-positive cells. Overall, carrimycin can kill pathogens directly while enhancing the host's immune response and indirectly killing bacteria. The normal WBC count was achieved in the patient after the application of carrimycin, and we speculate that carrimycin has a WBC count-increasing effect, which enhances host immunity by flipping the host's immune switch, thus eradicating pathogens. Thus, carrimycin is a novel therapeutic option for patients with APL and TB. Carrimycin also shows broad-spectrum antiviral efficacy against human coronaviruses (HCoVs) by targeting the post-entry replication event and inhibiting HCoV RNA synthesis^[10]. Moreover, it has potential antitumor activity through the inhibition of protein synthesis to regulate cell physiology, proliferation, and immunity^[13]. Cui *et al*^[14] found that the main component of carrimycin, isovalerylspiramycin I, suppresses tumorigenesis and metastasis. It is effective in the treatment of non-small cell lung cancer, head and neck tumors, and hepatocellular carcinoma^[15]. Therefore, we speculated that carrimycin also exerts an inhibitory effect on hematological tumors.

CONCLUSION

Herein, we report a case of APL combined with PTB. Given that the patient's WBC count continued to decrease, we added carrimycin to the PTB treatment and achieved excellent therapeutic outcomes. This study provides a reference for the treatment of patients with APL and TB. The therapeutic efficacy of carrimycin in APL accompanied by PTB requires further investigation.

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