Case Report

Penicilliosis marneffei in HIV negative children: three case reports

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Abstract: This study aimed to report the clinical characteristics of penicilliosis marneffei (PSM) in three children negative to HIV. Three children were diagnosed with PSM in the Department of Emergency Medicine, Hunan Children's Hospital between February 2016 to July 2020. The clinical characteristics, laboratory findings, and concomitant diseases were recorded, and the related literatures were reviewed. The clinical characteristics and treatment of PSM were reported according to our experience and literature review. The initial symptom was right lower limb mass in 1 child (first) who developed fever and cough about 1 month later and then was misdiagnosed with tuberculosis. The other child (second) had a fever, reductions in red blood cells, white blood cells and platelets, hepatosplenomegaly and lymphadenectasis. The third child had fever, jaundice, multiple organ dysfunction syndrome (MODS), hepatosplenomegaly and lymphadenectasis. The first child (Case 1) had STAT1 gene mutation on genetic examination, and the second child (Case 2) had history of onychomycosis and oral ulcer, the third child (Case 3) had STAT3 gene mutation on genetic examination, diagnosed with Hyperimmunoglobulin E syndromes (HIES). PSM was confirmed in all cases by the culture bone marrow. All three cases were diagnosed through medulloculture. Case 1 and Case 2 also had lymph node biopsy. Case 3 had sputum culture and bronchoalveolar lavage fluid (BALF). The first child was intravenously administered with voriconazole and amphotericin B liposomes, and orally administered with itraconazole for maintenance therapy, which was discontinued 1 year later. The second child was administered with voriconazole intravenously and thereafter orally for a total of 7 months. Recurrence was not observed. The third child was given amphotericin B for 2 days (discontinued due to liver dysfunction), and intravenous voriconazole for 4 days. The patient gave up therapy finally. In conclusion, HIV negative children can also develop PSM, and may be related to the STAT1/STAT3 gene mutation. For children having no response to antibiotic or antiviral therapy, bacterial/fungal culture or biopsy should be performed as soon as possible to confirm the diagnosis, and physicians should actively identify the underlying diseases of PSM patients, which is beneficial for the early diagnosis, early treatment and improvement of prognosis

Keywords: Penicilliosis marneffei (PSM); STAT1/STAT3 gene mutation; HIV negativity; child

Submitted Oct 17, 2020. Accepted for publication Mar 25, 2021.
doi: 10.21037/apm-20-2056
View this article at: http://dx.doi.org/10.21037/apm-20-2056

Introduction

Penicilliosis marneffei (PSM) is a rare deep fungal disease caused by Penicillium marniffei (PM). It is frequently found in HIV-positive or immunosuppressive patients (1), subjects with normal immunity are not likely to develop PSM, and it is even rarer in children (2). PSM mainly involves the mononuclear macrophages, its clinical manifestations are complex with a high mortality, and thus it is often misdiagnosed. In recent years, the incidence of invasive fungal infections is increasing in children, disseminated PSM is rarely reported, and the disseminated PSM related to immunodeficiency due to STAT1 and STAT3 gene mutation is even rarer in children. In the past 4 years, 3 HIV negative children were diagnosed with disseminated PSM in our hospital. Herein, we reported our experience

on the early diagnosis and differential diagnosis of PSM after reviewing literatures, which may provide evidence for future diagnosis of PSM in children. We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2056).

Case presentation

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

General characteristics

Case 1 (*Table 1*): a 2-year-old male had right lower limb mass about 2 months ago and developed recurrent fever and cough 20 days ago. His mother found a mass sized 6 cm × 5 cm at the right lower limb about 2 months ago. The mass was hard and had no redness and no ulcer. The skin on the tumor gradually became blue and purple, and then he visited the local hospital but did not improve. Twenty days ago, he developed fever and the highest body temperature reached 40.3 ℃, accompanied by cough and wheezing. He was suspected with tuberculosis on chest CT, and then HRZE was administered for anti-tuberculotic treatment without therapeutic efficacy. But the symptoms did not improve, skin test with PPD and tuberculosis-related T cell examination showed negative to mycobacterium tuberculosis. Then, this patient was transferred into our department. On physical examination, the patient was conscious, but malnutritional; multiple enlarged lymph nodes were noted, the neck could move freely, moist rales were noted in both lungs on auscultation; the heart rate was 130 beats/min, pot belly and thin subcutaneous fat were observed, liver localized 5 cm below ribs with hard texture, and the spleen was not accessible; a mass sized 5~6 cm was found near the right ankle; the mass was hard, had no tenderness and redness, and the extremities were warm. Results of laboratory examination were shown in *Table 1*. Enhanced chest CT showed pulmonary tuberculosis with bloodborne dissemination and fungal infection (*Figure 1*); bronchoscopy showed the granulomatous hyperplasia which obstructed the opening of right middle trachea with mucosal erosion and necrosis; The low limb CT showed a mass at the middle and lower segments of the right fibula, suggesting infectious lesions with pathological fracture. Findings after lymph node biopsy were consistent with fungal infection. Bone marrow culture in our hospital and another hospital showed Marneffe penicillin (*Figure 1*).

Case 2 (*Table 1*): a girl aged 4 years and 10 months was admitted due to fever and cough for 14 days. She developed fever as high as 40.2 ℃, and occasional cough was present. She visited local hospital 9 days ago, and routine blood test showed white blood cell count was 3.97×10^9/L; hemoglobin was 80 g/L; and total platelet count was 92×10^9/L. Thereafter, she received anti-infective for 8 day and IVIG treatment for 2 day. However, she still had a fever and a cough and then transferred into our hospital. She had a poor physical fitness, and recurrent onychomycosis was present after 2 years. There was a history of repeated oral ulcers and a history of long-term use of Chinese medicine. On physical examination, she was conscious with anemic appearance; palpable beaded lymph nodes were found above the left clavicle with poor mobility, unclear borders and partial fusion; the neck could move freely; moist rales were noted on auscultation; the heart rate was 100 beats/min; pot belly was observed, the liver was touched 4.5 cm below the ribs, the spleen was 7.5 cm below the ribs with hard texture. Laboratory examination results were shown in *Table 1*. Chest and abdomen CT showed splenomegaly, and uneven enhancement of undefined nodules in the spleen; pulmonary infection (fungal infection or tuberculosis) (*Figure 2*); findings after lymph node biopsy were consistent with those of fungal lymphadenitis (*Figure 2*). Bone marrow culture and sputum fungus culture showed Marneffe penicillin.

Case 3 (*Table 1*): a female girl aged 2 years was admitted due to abdominal distension for 6 months, fever for 15 days, icteric sclera for 7 days, and cough for 4 days. She developed abdominal distension 6 months ago. But no attention was paid to. She had fever 15 days ago with the highest temperature of 39.9 ℃. She was given oral medicine without improvement. She then developed jaundice 1 week ago, and paroxysmal cough with exacerbated abdominal distension and jaundice 4 days ago. She was admitted in a local hospital and treated for 4 days without any improvement. On physical examination, she was conscious with jaundice and icteric sclera. No palpable lymph node was found. The respiratory rate was slightly increased, and moist rales were noted in both lungs on auscultation. Abdomen was distent. The liver was 6.5 cm below the ribs, the spleen was 4.5 cm below the ribs with hard texture. CRT was 1–2 s. Laboratory examination was shown in *Table 1*: IL-6

Table 1 General information of cases 1, 2 and 3

Items	Case 1	Case 2	Case 3
Age	2 years	4 years 10 months	2 years
Gender	Male	Female	Female
Chief complaint	Right lower extremity mass for 2 months with recurrent fever and cough for 20 days	Fever with cough for 14 days	Abdominal distension for 6 months, fever for 15 days, jaundice for 7 days, and cough for 4 days
Positive sign	Multiple superficial lymph nodes enlargement, liver 4 cm below rib, 5 cm × 6 cm mass in right lower lib	Multiple superficial lymph nodes enlargement, liver 4.5 cm below rib, spleen 7.5 cm below rib	Jaundice, superficial lymph nodes no enlargement, liver 6.5 cm below rib, spleen 4.5 cm below rib
Past history	Recurrent respiratory tract infection	Recurrent leukonychia and oral ulcer	Poor living condition
White blood cell	6.23×10^9/L	2.94×10^9/L	7.34×10^9/L
Neutrophil	0.531	0.528	0.807
Hemoglobin	103 g/L	77 g/L	86 g/L
Platelet	162×10^9/L	81×10^9/L	40×10^9/L
Erythrocyte sedimentation rate	62 mm/h	26 mm/h	2 mm/h
Procalcitonin	2.07 ng/mL	8.01 ng/mL	14.38 ng/mL
C-reactive protein	48.70 mg/L	18.5 mg/L	38.37 mg/L
Serum ferritin	906 ng/mL	222.3 ng/mL	1,390.0 ng/mL
Alanine aminotransferase	202.10 IU/L	79.6 IU/L	246.60 IU/L
Aspartate aminotransferase	518.40 IU/L	125.3 IU/L	1,099.90 IU/L
Albumin	25.50 g/L	26.8 g/L	22.9 g/L
Mycoplasma pneumoniae	1:160(+)	(–)	(–)
Fungus 1-3-β-D Dextran	<10 pg/mL	2,327.1 pg/mL	118.1 pg/mL
Aspergillus antigen test	0.495	0.688	1.383
Immune function	(–)	C3 0.41 g/L, C4 0.14 g/L,	IgE 1,620.00 IU/mL
Lymphocyte subgroup	Th/Ts(CD4+/CD8+) 0.82	NK 7.11	T cell 46.85%, B cell 50.21%, NK 2.28%
Blood culture	(–)	(–)	*Streptococcus pneumoniae*
Medulloculture	*Penicillium marneffei*	*Penicillium marneffei*	*Penicillium marneffei*
Sputum culture	(–)	(–)	(–)
Sputum fungus culture	(–)	*Penicillium marneffei*	*Penicillium marneffei* (Sputum and BALF)
T-SPOT	(–)	(–)	(–)
EBV-DNA fluorescent quantitation	Normal	Normal	Normal
ANA+ANA spectrum+ANCA	(–)	(–)	(–)

Table 1 (*continued*)

Table 1 (*continued*)

Items	Case 1	Case 2	Case 3
Chest CT	Middle lobe caseous pneumonia	Diffuse nodosus shadow in both lungs	Multiple patchy high-density shadow in both lungs
Echocardiography	(–)	(–)	(–)
Abdominal+cervical ultrasound	Lymph node enlargement, liver enlargement	Lymph node enlargement, liver and spleen enlargement	Lymph node no enlargement, liver and spleen enlargement
Bone marrow hemocytology	Significant active bone marrow hyperplasia	Significant active bone marrow hyperplasia, visible toxic granulation	Significant active bone marrow hyperplasia, visible toxic granulation
Lymph node biopsy	(Right inguinal hernia) fungal spore structure, PAS(+)	(Left supraclavicular area) vast fungal spore structure, fungal immunofluorescence staining and PAS(+)	Not done
Genetic testing	STAT1 gene mutation	Not done	STAT3 gene mutation (high IgE syndrome)
Treatment	Intravenous voriconazole for 2 weeks, amphotericin B for 3 weeks, oral itraconazole for 1 year	Intravenous voriconazole for 3 weeks, oral voriconazole for 7 months	Amphotericin B for 2 days (discontinued due to liver insufficiency), Intravenous voriconazole for 4 days
Follow-up	No complaints	No complaints	Give up and die

T-SPOT, T cell spot detection of tuberculous infection; EBV-DNA, Epstein-Barr virus deoxyribonucleic acid; ANA, antinuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; CT, computerized tomography.

202.93 pg/mL; IL-10 38.87 pg/mL; IFN-γ 30.67 pg/mL; NH4 121.8 μmol/L; D-Dimer 11.29 μg/mL; PT 16.8 s; FIB 119 mg/dL; TT 23.5 s; AT3 34%; FDP 27.25 μg/mL; TBIL 110.10 μmol/L; DBIL 88.90 μmol/L; IBIL 21.20 μmol/L; BALF sputum smear PAS(+), fungal spores seen with microscope with some buds. Chest and abdomen CT showed multiple patchy opacities in both lungs, and diffused low density patch in liver and spleen: systemic inflammatory disease with organ dysfunction or hematological disease? (*Figure 3*). Genetic examination results showed STAT3 gene mutation, diagnosed with Hyperimmunoglobulin E syndromes (HIES). Bone marrow culture, sputum fungus culture and BALF all showed Marneffe penicillin.

Treatments

In case 1, voriconazole was administered at 6 mg/kg (Q12h) in the first day and at 4 mg/kg (Q12h) in the second day for a total of 2 weeks. Then, amphotericin B liposome was employed for antifungal therapy due to the poor therapeutic efficacy. It was initially administered at 0.1 mg/kg, and then the dose was increased by 0.1 mg/kg per day until the dose of amphotericin B liposome reached 0.5 mg/kg. This patient received amphotericin B for 3 weeks, accompanied by liver protection and other treatments. The disease condition was improved and he was discharged (*Figure 4*). Follow-up: after discharge from the hospital, he took oral itraconazole 5 mg/kg/d (twice daily) for 1 year. The mass of right lower limb gradually disappeared. After repeated fungal cultures of alveolar lavage fluid and bone marrow showed negative, this patient received anti-fungal treatment for additional 6 months. After 1-year treatment, treatment was discontinued, this patient received follow-up, but recurrence was not observed. He occasionally had a cold and had general physical fitness. He was waiting for the hematopoietic stem cell transplantation. In case 2, voriconazole was initially administered at 6 mg/kg (Q12h) in the first day and thereafter at 4 mg/kg (Q12h) for anti-fungal therapy for a total of 4 weeks. Amphotericin B was not used due to economic concern. The body temperature returned to normal 2 days later, and she was discharged when the disease condition was improved. Follow-up: after discharge

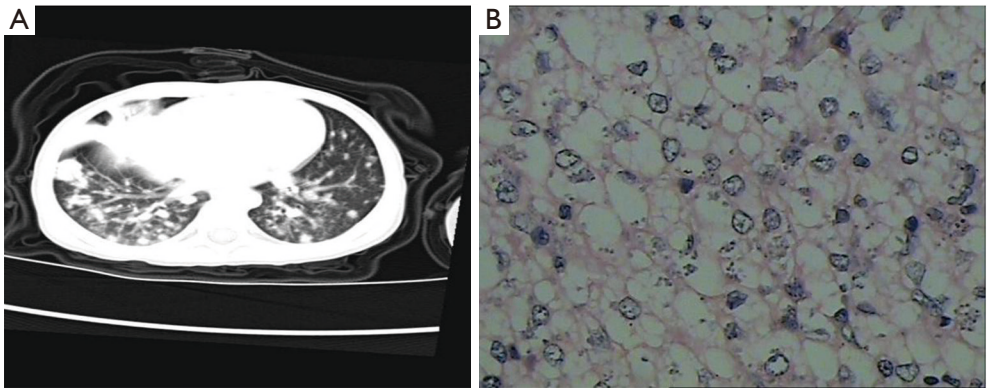

Figure 1 (A) Case 1. Lung CT showed the patchy and spotty high-density shadow with diffuse distribution and nodules of different sizes. (B) Case 1. Pathological examination after lymph node biopsy showed fungal spores in the tissue cells [fluorescence immunostaining and PAS staining of fungi (+)]. HE, ×400.

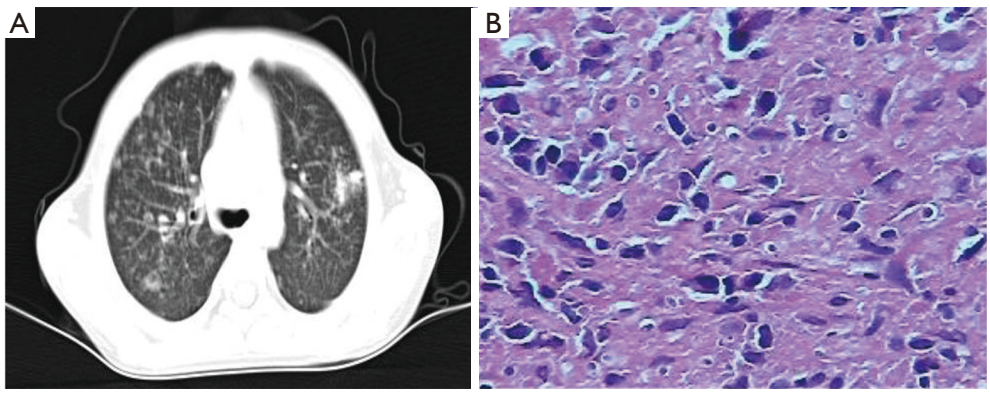

Figure 2 (A) Case 2. Lung CT showed diffuse distribution of small nodules in both lungs. (B) Case 2. Pathological examination after lymph node biopsy showed a large number of fungal spores in the tissue cells [fluorescence immunostaining and PAS staining of fungi (+)]. HE, ×400.

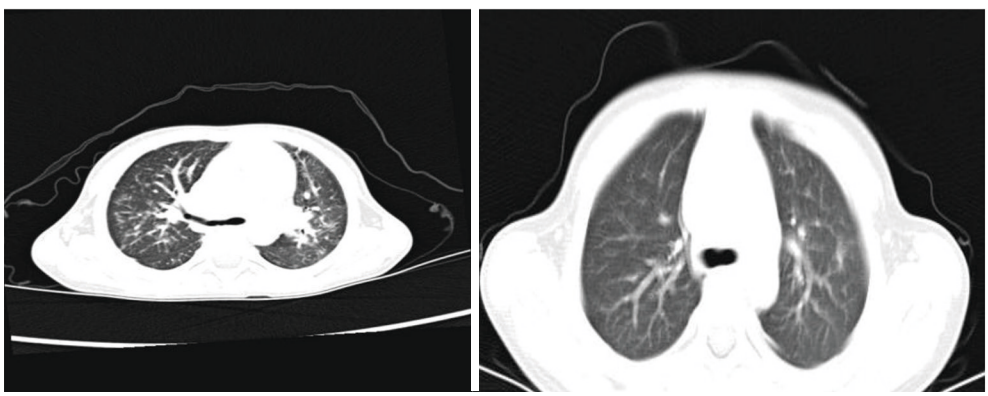

Figure 3 Case 3. Lung CT showed multiple patchy high-density shadow with blur edge in both lungs, and air bronchogram.

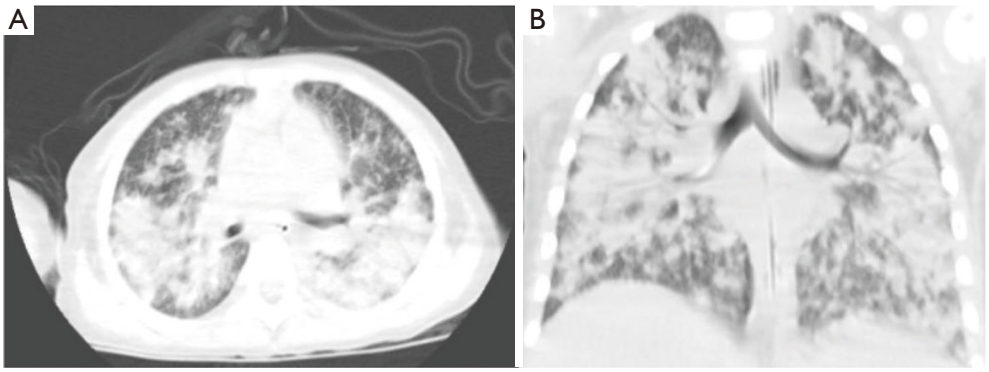

Figure 4 (A) Case 1. Lung CT showed the patchy high-density and strip-shaped shadow as well as nodules, which were improved significantly. (B) Case 2. Reexamination by lung CT showed a few light patchy shadows in the upper lobe of the left lung, but nodules were absent.

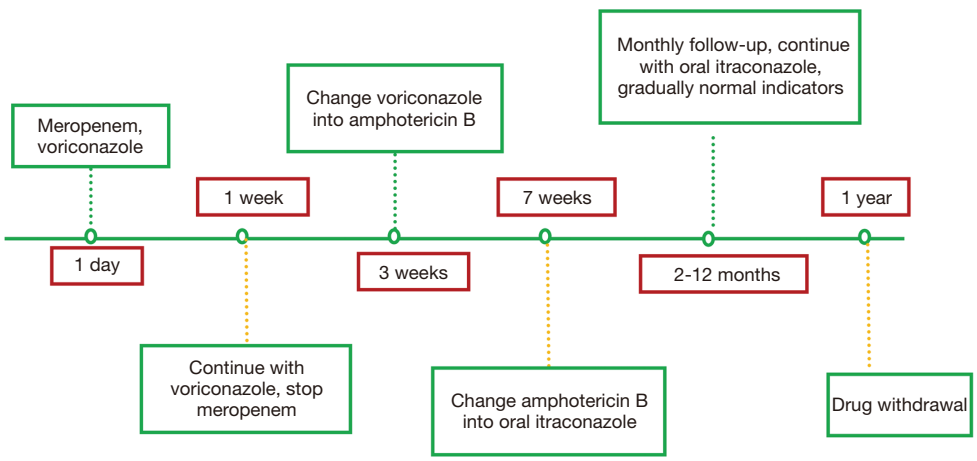

Figure 5 Timeline of Case 1.

from the hospital, oral voriconazole was administered at 4 mg/kg (Q12h) for 6 months. Repeated examinations showed negative, lung CT showed the disappearance of lung lesions (*Figure 4*); the abdominal color ultrasonography did not find the spleen and liver below the ribs. The treatment was discontinued after 7-month treatment. Currently, the child had no discomfort and side effects of anti-fungal therapy were not present (*Figures 5*,*6*). The third child was given amphotericin B for 2 days which was discontinued due to liver insufficiency, and intravenous voriconazole for 4 days. The child was given mechanical ventilation, hemodialysis, plasmapheresis and plasma cryoprecipitate and platelet supply due to MODS. The child died after the parents gave up therapy.

Genetic examination

In case 1, genetic examination was done, and results showed STAT1 gene mutation. In case 2, genetic examination was not done due to economic concern. In case 3, genetic examination results showed STAT3 gene mutation, diagnosed with HIES.

Literature review

Penicillium/Penicilliosis Marneffei or Talaromycosis/Talaromyces marneffei were used as terms to search the Chinese database (Wanfang Med Online and CNKI) between January 2010 and January 2020. A total of 484

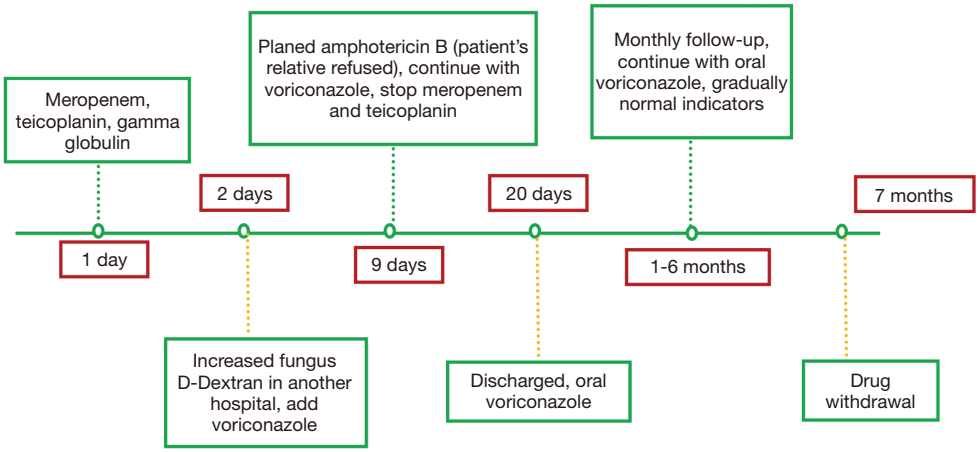

Figure 6 Timeline of Case 2.

literatures were identified, in which there were 23 literatures related to children, including 21 case reports. Then, Penicillium marneffei and Talaromyces marneffei were used as terms to search the PubMed, and a total of 340 literatures were identified, in which 24 literatures were related to children including 10 case reports. Of note, most English literatures were from China. Herein, we summarized the clinical and laboratory characteristics of PSM.

PSM was diagnosed in a total of 53 HIV-negative children with the age ranging from 3 months to 13 years. The clinical characteristics of all PSM children reported in the literature see *Table 2* for details.

There were 36 boys (67.9%). In most children, respiratory symptoms were the initial manifestations (n=30; 56.6%); the initial manifestation was also found as the neurological system symptoms (n=4; 7.55%), rash (n=4; 7.55%), neck mass (n=3; 5.66%) and lower limb mass (n=1; 1.89%). In addition, 6 children had concomitant hemophagocytic syndrome. Forty-five children had fever (84.9%), 7 had rash (pustules or nodules) (13.2%), 35 had hepatomegaly (69.8%), 30 had splenomegaly (56.6%) and 30 had lymphadenectasis (56.6%). Five children were misdiagnosed as having pulmonary tuberculosis (9.43%). Medical history: X-linked high IgM was found in 6 patients, recurrent oral ulcer in 4, recurrent pneumonia in 4, Hirschsprung's disease in 2, premature delivery in 2 and tuberculosis in 2. Moreover, high IgE syndrome, G-6PD enzyme deficiency, leukemia, chickenpox and cystadenomatous malformation of left lower lung with infection were found in 1 patient, respectively. Methods for confirmed diagnosis: PSM was confirmed in 24 by bone marrow culture (45.3%), in 23 by blood culture (43.4%), in 16 by lymph node biopsy (30.2%), in 8 by alveolar lavage fluid culture (15.1%), in 4 by lung biopsy (7.55%), and in 2 by sputum fungal culture (3.77%). Culture of cerebrospinal fluid, peritoneal puncture fluid, skin, and mass secretions was employed to confirm the diagnosis of PSM in 1 patient, respectively; the biopsy of bronchial intima, skin, and brain tissues was done to confirm the diagnosis of PSM in 1 patient, respectively. Treatments: voriconazole was used in 14 patients, amphotericin B liposome + itraconazole in 11, voriconazole + itraconazole in 8, amphotericin B liposome + voriconazole in 4, amphotericin in 3, fluconazole in 3, itraconazole in 2, and amphotericin + fluconazole in 1, and 7 children were not treated. Prognosis: improvement was noted in 32 patients (60.4%) and death in 21 (39.6%).

Discussion

Talaromycosis is a deep fungal infection caused by *Talaromyces marneffei* (*T. marneffei*). It is often found in HIV positive patients, and several studies have reported disseminated PSM in children (3). The non-specific clinical manifestations usually cause misdiagnosis and missed diagnosis in clinical practice (4). Talaromycosis is a common opportunistic infection. *T. marneffei* is the only Biophase Penicillium that can cause diseases in humans, and an important pathogenic thermoeform fungus in Southeastern Asia (5). Inhalation of aerosolized conidia from environmental sources is the main route of infection and propagation (6). In 2011, *T. marneffei* was renamed as PM (7). PSM progresses rapidly with a high mortality.

Table 2 Clinical characteristics of all PSM children reported in the literature

Gender	Boy (n=36; 67.9%)	Girl (n=17; 32.1%)	
Initial manifestation	Respiratory symptoms (n=30; 56.6%)	Neurological system symptoms (n=4; 7.55%)	Rash (n=4; 7.55%)
	Neck mass (n=3; 5.66%)	Lower limb mass (n=1; 1.89%)	Concomitant hemophagocytic syndrome (n=6; 11.3%)
Clinical feature	Fever (n=45; 84.9%)	Rash (pustules or nodules) (n=7; 13.2%)	Hepatomegaly (n=35; 69.8%)
	Splenomegaly (n=30; 56.6%)	Lymphadenectasis (n=30; 56.6%)	Misdiagnosed as pulmonary tuberculosis (n=5; 9.43%)
Medical history	X-linked high IgM (n=6; 11.3%)	Recurrent oral ulcer (n=4; 7.55%)	Recurrent pneumonia (n=4; 7.55%)
	Hirschsprung's disease (n=2; 3.77%)	Premature delivery (n=2; 3.77%)	Tuberculosis (n=2; 3.77%)
	High IgE syndrome (n=1; 1.88%)	G-6PD enzyme deficiency (n=1; 1.88%)	Leukemia (n=1; 1.88%)
	Cystadenomatous malformation of left lower lung with infection (n=1; 1.88%)	Chickenpox (n=1; 1.88%)	
Methods for confirmed diagnosis	Bone marrow culture (n=24; 45.3%)	Blood culture (n=23; 43.4%)	Lymph node biopsy (n=16; 30.2%)
	Alveolar lavage fluid culture (n=8; 15.1%)	Lung biopsy (n=4; 7.55%)	Sputum fungal culture (n=2; 3.77%)
	Cerebrospinal fluid culture (n=1; 1.88%)	Peritoneal puncture fluid culture (n=1; 1.88%)	Mass secretions culture (n=1; 1.88%)
	Skin secretions culture (n=1; 1.88%)	Bronchial intima biopsy (n=1; 1.88%)	Skin biopsy (n=1; 1.88%)
	Brain tissues biopsy (n=1; 1.88%)		
Treatment	Voriconazole (n=14; 26.4%)	Amphotericin B liposome + itraconazole (n=11; 20.8%)	Voriconazole + itraconazole (n=8; 15.1%)
	Amphotericin B liposome + voriconazole (n=4; 7.55%)	Amphotericin (n=3; 5.66%)	Fluconazole (n=3; 5.66%)
	Itraconazole (n=2; 3.77%)	Amphotericin + fluconazole (n=1; 1.88%)	Not treated (n=7; 13.2%)
Prognosis	Improvement (n=32; 60.4%)	Death (n=21; 39.6%)	

Therefore, rapid and accurate diagnosis is crucial for the improvement of the prognosis of children (8). PM usually invades the human body through the lung, which is often the primary organ for systemic disseminated infection. PSM can also be spread through the reticuloendothelial system, resulting in lymphadenectasis, hepatosplenomegaly, and reductions of blood cells. In case 2 and case 3, fever and cough were present, but the symptoms and signs of the lung were not evident while lung CT showed significant changes. Therefore, early lung CT is helpful for the clinical diagnosis. PSM has no specific clinical manifestations and is easily misdiagnosed as cryptococcosis or tuberculosis, which brings difficulties to the clinical diagnosis of PSM. Currently, the typical clinical manifestations of PM infection in HIV-negative patients are still unclear (2). Qiu *et al.* (9) found that 31.1% of among HIV-negative patients with PM infection and pleural effusion were misdiagnosed as tuberculosis and received long-term anti-tuberculotic treatment. Fungal culture or histopathological examination is the gold standard for the diagnosis of PSM (10). In the present report, the initial symptom was lower limb mass in case 1, followed by respiratory symptoms. This patient was misdiagnosed with tuberculosis. In case 2, she had fever, hepatosplenomegaly and reductions in blood cells,

highly suggesting hematological diseases. In case 3, she had fever, jaundice, MODS, hepatosplenomegaly and lymphadenectasis. Three patients were confirmed to have PSM by bone marrow culture. Case 1 and case 2 also had lymph node biopsy. Case 2 had sputum fugal culture. Case 3 had sputum fugal culture and BALF culture. Therefore, if the patient is non-responsive to the treatment, early culture or tissue biopsy should be performed as soon as possible to confirm the diagnosis. In case 2 and case 3, both G test and GM test showed increases, but they showed normal in case 1. Thus, invasive fungal infection can't be determined based on G test and/or GM test, and clinical characteristics should be taken into account.

PSM is often found in HIV patients, but it has also been reported in HIV-negative patients, indicating that PSM patients who are HIV-negative and have no secondary immunodeficiency may have potential unrecognized immunodeficiency. Therefore, genetic examination is necessary for HIV-negative children with invasive fungal infection. Studies have confirmed that HIV-negative patients with PSM often have immune dysfunction such as severe combined immunodeficiency, congenital neutrophil deficiency, HIES and high IgM syndrome (11,12). Defects of genes related to (IFN-γ)/STAT1 signaling pathway and STAT3-mediated Th17 differentiation may be related to the fungal infection in HIV-negative children (2,13). Lee *et al.* (14) found that the gain-of-function disorder of signal transduction and activator of transcription 1 (STAT1) was a potential cause of invasive fungal disease in children. Zeng *et al.* (11) reviewed 7 cases of HIV negative children with PSM, and 5 patients had underlying diseases such as recurrent pneumonia, mycotic stomatitis and hemophagocytic syndrome. In a study, 15 patients were diagnosed with invasive fungal infection in 19 patients with immunodeficiency, including 10 patients with X-linked high IgM syndrome, 3 with HIES, 4 with acquired STAT1 disorder, and 2 with autosomal recessive IFN -γRI defect (15,16). In the available studies, nearly 50% of patients had underlying immune-related diseases of varying degrees, indicating that the PSM in most patients is related to immune deficiency or dysfunction. In our report, the immune function was normal in 3 children, and both T cell immunity and humoral immunity were normal. However, in case 1, genetic examination showed STAT1 gene mutation, and case 3, genetic examination showed STAT3 gene mutation (HIES), suggesting that PSM is related to gene mutation. In case 2, there was a history of repeated onychomycosis and oral ulcers, which are the characteristics of chronic skin and mucous Candida infection (CMC). STAT1 is an important factor in multiple signal transduction pathways, and STAT1 gene mutation may lead to the primary immunodeficiency (PID) (17,18). In patients with gain-of-function STAT1 gene mutation, 98% may develop CMC infection (19). The presence of invasive fungal infection or cancer predicts a poor prognosis (20). In our report, the child with STAT1 and STAT3 gene mutation had no prior CMC infection, while the second child had clinical features of prior CMC infection. Few studies have reported the invasive fungal infection caused by STAT1 gene mutation. Gan *et al.* (21) reported 5 cases of chronic mucocutaneous candidiasis related to gain-of-function STAT1 gene mutation, but only 1 patient had invasive fungal infection. In case 1, he could be diagnosed with PSM related to STAT1 gene mutation. In 70–80% of patients with gain-of-function STAT1 gene mutation, the lymphocyte count, lymphocyte function and immunoglobulin level are in normal ranges. Currently, stem cell transplantation is the unique effective treatment for immunodeficiency disease caused by STAT1 gene mutation. Although HSCT is an effective treatment, its complications may cause reconstruction failure after transplantation, reducing the survival rate (22). HIES are rare PID diseases characterized by observably elevated serum immunoglobulin (Ig) E, recurrent pneumonia, and chronic eczema (15). Case 3 was diagnosed with HIES, which are caused by heterozygous mutations in STAT3, with significantly increased IgE. The child showed exacerbated chest CT. She did not have any history of recurrent pulmonary infection or chronic eczema. She had hepatosplenomegaly and MODS as her main manifestation. Thus, HIES should be considered when increased IgE and multiple organ impairment show up. Molecular and genetic diagnostic tests are important for case of suspected HIES.

Currently, there is no consensus on the treatment of PSM. Early diagnosis and effective, low-toxic, regular antifungal treatments are crucial for the treatment of PSM. Amphotericin B is the treatment of choice for PSM, which is often followed by sequential treatment with itraconazole (23). However, amphotericin B can cause serious adverse reactions such as liver and kidney damage and severe hypokalemia, which significantly limits its wide application in clinical practice. Voriconazole is a new broad-spectrum triazole antifungal drug, and can be used for the clinical treatment of PSM. Ouyang (24) investigated the safety and efficacy of voriconazole in the treatment of disseminated PM infection. They found that 10 of 14

patients had a complete remission after16-week treatment, 3 had a partial remission, and only 1 had no response, suggesting that voriconazole is an effective and well-tolerated treatment for PSM (25). In case 1, the patient was intravenously administered with voriconazole and amphotericin B liposomes, and then received maintenance therapy with oral itraconazole for 1 year. In case 2, the child was initially treated with voriconazole for 4 weeks, followed by treatment with oral voriconazole for additional 6 months, achieving favorable efficacy. In case 3, we also choose intravenous voriconazole as antifungal treatments considering liver dysfunction.

Conclusions

In summary, the clinical manifestations of PSM are complex and non-specific, which brings difficulties to the clinical diagnosis of PSM, causing misdiagnosis and missed diagnosis. Therefore, if the patient is non-responsive to antibiotic treatment and has multisystem injury of no cause, PSM should be considered. Early culture of blood, bone marrow or BALF and tissue biopsy (skin, lymph nodes, etc.) are important for confirmed diagnosis. Moreover, clinicians should attempt to identify the underlying diseases related to PSM (such as immunodeficiency-related gene examination), which is helpful for the early diagnosis and early treatment, and may reduce mortality and improve prognosis. At present, the diagnostic methods of PSM have been gradually improved. The genetic tests of causes of Marneffe, such as immunodeficiency, are getting more and more attention. However, which gene mutations or deletions related immunodeficiency are likely to suffer from Marneffe still needs a large-sampled research. The types of drugs, treatment time, and withdrawal indications for Marneffe treatment are still inconclusive. Due to the existence of immunodeficiency, patients may be prone to relapse. Thus, further investigation and research are needed.

Acknowledgments

Funding: This study was supported by 2019 National Medical Service and Support Capacity Improvement Project (Medical and Health Institution Capacity Building) and Key Laboratory of Pediatric Emergency Medicine of Hunan Provincial (2018TP1028).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2056

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2056). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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Cite this article as: Fan JH, Luo HY, Yang LG, Wang MY, Xiao ZH. Penicilliosis marneffei in HIV negative children: three case reports. Ann Palliat Med 2021;10(7):8437-8447. doi: 10.21037/apm-20-2056

