

Unmasking Immune Reconstitution Inflammatory Syndrome (IRIS) Associated with Disseminated Penicilliosis in an AIDS Patient: First Adult Case in Thailand

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ABSTRACT

A 16-year old Thai male with fever and weight loss for two weeks was diagnosed with AIDS (CD4 cell count 71 cells/mm³, HIV viral load 564,000 copies/mL). Complete blood count was normal, and blood cultures were negative. Antiretroviral therapy (ART) resulted in resolution of fever and weight gain. One week later, he developed a high fever, weight loss, jaundice, abdominal pain, and hepatosplenomegaly, but no umbilicated skin lesions or superficial lymphadenopathy. Investigations showed anemia, leukopenia, and transaminitis. CT scan demonstrated hepatosplenomegaly with microabscess formation and intra-abdominal lymphadenopathy. Hemocultures yielded *Talaromyces marneffe* (formerly *Penicillium marneffe*). Immune reconstitution inflammatory syndrome was suspected due to clinical deterioration after starting ART in a patient with low pretreatment CD4 cell count. This is the first report of an adult AIDS patient with penicilliosis-associated IRIS in Thailand. A literature review and summary of 14 previously reported cases are included.

Keywords: *Talaromyces marneffe*; *Penicillium marneffe*; Penicilliosis; Immune reconstitution inflammatory syndrome (IRIS) (Siriraj Med J 2017;69: 300-305)

INTRODUCTION

Disseminated penicilliosis is a potentially fatal systemic mycosis caused by the dimorphic fungal pathogen *Talaromyces marneffe* which usually develops in HIV-infected patients with advanced immunosuppression.¹ Penicilliosis is the fourth most common AIDS-related opportunistic infection (OI) in northern Thailand after tuberculosis, cryptococcosis, and *Pneumocystis jiroveci* pneumonia.² Immune reconstitution inflammatory syndrome (IRIS) is a condition which occurs in AIDS patients whose immune function is recovering after receiving antiretroviral therapy (ART).³ Clinical deterioration and exaggerated inflammatory reactions occur as a result of interactions between the improving immune system

and a formerly unrecognized pathogen. Only 14 cases of penicilliosis-associated IRIS have been reported. All patients had been living in or had traveled to Thailand, India, China, or Vietnam, which are endemic areas.

CASE REPORT

A 16-year-old male from northeastern Thailand presented in May 2005 with fever, fatigue, anorexia, and weight loss for two weeks. There was no lymphadenopathy, hepatosplenomegaly, or skin lesions. Complete blood count (CBC) and liver function tests (LFTs) were normal, and hemocultures were negative. He was diagnosed with AIDS (CD4 cell count 71 cells/mm³, HIV viral load 564,000 copies/mL) at a hospital in Bangkok. ART

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(lamivudine, stavudine, efavirenz) resulted in resolution of fever and weight gain.

One week after commencing ART, the patient developed a high fever, jaundice, and right upper abdominal pain with localized peritonitis. LFTs were abnormal (direct bilirubin 5.2 mg/dL, AST 215 U/L, ALT 113 U/L, ALP 1,276 U/L). Contrast-enhanced CT scan showed hepatosplenomegaly with microabscess formation, intra-abdominal lymphadenopathy, and ascites (Fig 1). Diagnostic laparoscopy revealed congestion of liver and spleen, although tissue biopsy was not obtained. Peritoneal fluid analysis was as follows: microscopy - total cell count 2,900 cells/mm³, WBC count 395 cells/mm³ (PMN 45%, L 30%); cytology - negative; microbiology - all negative (Gram's, acid-fast, and modified acid-fast stains; cultures for bacteria and fungus, and culture and PCR for *Mycobacterium tuberculosis* complex). Serum cryptococcal antigen and PCR for cytomegalovirus (CMV) were negative. ART was suspended, and empirical treatment for disseminated tuberculosis and *Mycobacterium avium* complex (MAC) infection was started (isoniazid, ethambutol, clarithromycin, levofloxacin, amikacin). One week later, there was persistent fever, abdominal pain, and weight loss. Isoniazid was discontinued due to worsening of LFTs (AST 485 U/L, ALT 185 U/L).

On admission to the authors' hospital, physical examination showed fever, cachexia, pallor, jaundice, hepatosplenomegaly, and pruritic papular eruptions at lower extremities, but no oral thrush or ulcers, umbilicated papules, or superficial lymphadenopathy. CBC and LFTs were abnormal (hemoglobin 7.9 g/dL, WBC count 2,300 cells/mm³, platelet count 261,000 cells/mm³, direct bilirubin 3.7 mg/dL, AST 424 U/L, ALT 153 U/L, ALP 1,139 U/L). Chest x-ray was normal. Treatment included ethambutol, clarithromycin, levofloxacin, amikacin, trimethoprim-

sulfamethoxazole, and fluconazole.

On day five, two sets of hemocultures were positive for "non-septate hyphae" by Gram's stain. Amphotericin B deoxycholate 0.7 mg/kg/day was started. Subculture in Sabouraud Dextrose Agar at 25°C for six days yielded blue-green colonies surrounded by red pigment. Lactophenol cotton blue wet mount preparation demonstrated septate hyphae with characteristic broom-shaped conidiophores and conidia, leading to the diagnosis of *T. marneffei* infection. Intravenous amphotericin B was given for two weeks, followed by itraconazole 400 mg/day for 10 weeks. At six weeks, there was resolution of fever and abdominal pain, weight gain, and normalization of LFTs. ART was then resumed. HIV viral load was 880 copies/mL three months later. He was given itraconazole 200 mg/day until achievement of CD4 ≥ 100 cells/mm³ for six months. In 2014, his CD4 count was 1,045 cells/mm³. His viral load was < 40 copies/ml. No relapse of penicilliosis has occurred.

DISCUSSION

The diagnosis of HIV-associated IRIS usually requires most of the following key features^{3,4}: (1) A temporal relationship between ART commencement and onset of clinical deterioration (several days to six months). Clinical manifestations of OIs may be unusual or of greater intensity. (2) Signs of local (swelling, lymphadenitis) or systemic inflammation (fever, tachycardia, tachypnea, leukocytosis / leukopenia). (3) A low pretreatment CD4 cell count, usually < 100 cells/mm³. (4) Evidence of immunological recovery: increase in CD4 cell count and/or decline in HIV viral load. (5) Exclusion of other causes: adverse drug reactions (e.g. abacavir hypersensitivity reaction), newly acquired OIs, and failure of ART. IRIS may present in two ways.^{3,4} Paradoxical IRIS occurs



Fig 1. Disseminated penicilliosis in a 16-year old male with AIDS. (A) Contrast-enhanced coronal CT image shows hepatosplenomegaly and multiple hypodense nodules in the spleen, suggestive of microabscess formation. (B, C) Contrast-enhanced axial CT images show hepatosplenomegaly and intra-abdominal lymphadenopathy.

TABLE 1. Summary of previously reported cases of penicilliosis-associated IRIS in HIV-infected patients.

Case	Country, year reported, author	Age (yr), Sex	Status prior to starting ART	Immune status ART	IRIS type, Time to onset	Clinical, investigations	Status at diagnosis of penicilliosis-associated IRIS	Treatment	Outcome
			Clinical, investigations	Immune status ART		Clinical, investigations	Immune status		
1	India, 2007, Gupta S et al. ⁹	35, M	Fever, diarrhea, weight loss, hepatosplenomegaly, herpes genitalis, anemia, H/C -	CD4 4, VL-NA d4T, 3TC, NVP	Unmasking 4 wk	Cervical, axillary lymphadenopathy, hepatosplenomegaly, no fever / cough / skin lesions, pancytopenia, LN biopsy and culture +, H/C +	CD4-NA VL-NA	AmphoB 0.6 MKD x 14 d, then Itra 400 mg/d x 10 wk, then 200 mg/d	At 10 mo: liver and spleen not palpable, weight gain, regression of LN, CD4 224
2	India, 2009, Saikia L et al. ¹⁰	12, M	Fever, cough, diarrhea, weight loss, oral thrush, umbilicated skin lesions, anemia, skin biopsy and culture +, H/C -, Rx Itra 400 mg/d	CD4 11, VL-NA d4T, 3TC, EFV started same time as Itraconazole	Paradoxical 4 wk	Fever, arthritis, lymphadenopathy, exacerbation of skin lesions, skin biopsy and culture NA, H/C +	CD4 172 VL-NA	NA	NA
3	India, 2010, Saikia L et al. ¹¹	28, M	Fever, cough, diarrhea, weight loss, oral thrush, anemia, leukopenia, H/C NA	CD4 47, VL-NA d4T, 3TC, NVP	Unmasking 2 wk	Scaly papules / nodules with central necrosis on face, extremities, scrotum, skin biopsy and culture +, H/C -	CD4 160 VL-NA	AmphoB 0.6 MKD x 1 dose, then Itra 400 mg/d x 8 wk, then 200 mg/d	At 2 mo: skin lesions resolved completely, weight gain
4	UK (traveled to Thailand), 2010, Ho A et al. ¹²	39, M	Fever, diarrhea, weight loss, molluscum contagiosum-like lesions on face, PJP, anemia, leukopenia, skin biopsy NA, H/C -	CD4 72, VL 3,800,000 TDF, FTC, EFV	Unmasking 4 wk	Enlargement of facial lesions, nodules on extremities, forehead wound with pus (injury with soil contact), pus culture +, skin biopsy and H/C NA	CD4 273 VL 3 log drop	AmphoB 0.6 MKD x 14 d, then Itra 600 mg/d x 10 wk, then 200 mg/d x 4 mo	At 2 mo: skin lesions resolved, weight gain At 28 mo: no recurrence, CD4 375, VL < 40
5	Thailand, 2012, Sudjaritruk T et al. ¹³	14, F	Fever, anorexia, weight loss, PJP, herpes zoster on trunk, H/C NA	CD 39, VL-NA d4T, 3TC, NVP	Unmasking 8 wk	Fever, arthritis, generalized umbilicated papules / nodules, oral ulcers, anemia, skin biopsy +, skin culture -, H/C -	CD4 51 VL < 50	AmphoB 0.7 MKD x 14 d, then Itra 10 MKD x 10 wk, then 5 MKD x 4 mo	At 1 mo: skin lesions and arthritis resolved At 1 yr: weight gain, CD4 269, VL < 50
6	UK (traveled to Thailand), 2013, Hall C et al. ¹⁴	62, M	Fever, weight loss, follicular skin lesions, esophageal candidiasis, disseminated MAC infection, pancytopenia, H/C NA	CD4 16, VL 263,000 TDF, FTC, EFV	Unmasking 12 wk	Fever, weight loss, nodules on trunk and arms, epigastric mass, CT scan: intra-abdominal lymphadenopathy, hepatosplenomegaly, skin culture +, intraabdominal LN culture +, H/C+	CD4 29 VL 47.3	Liposomal amphotericin B 1 MKD x 21 d, then Itra 400 mg/d	At 1 mo: weight gain, hepatomegaly and lymphadenopathy resolved, CD4 53, VL < 34
7	India, 2015, Bachaspatimayum R et al. ¹⁵	40, M	7 yr ago cervical LN biopsy +, Rx Itra x 9 mo, lymphadenopathy resolved Presented with few papules on nose, skin biopsy and H/C NA	CD4 57 VL 389,000 TDF, 3TC, ATV/r*	Unmasking 2 days	Rapid, generalized spread of umbilicated, ulceronecrotic skin lesions, hepatomegaly, anemia, skin biopsy +, skin culture and H/C NA	CD4 140 VL-NA	Itra 400 mg/d x 12 wk, then 200 mg/d x 6 mo	At 3 mo: skin lesions completely resolved
8	India, 2015, Rama SK et al. ¹⁶	33, M	Weight loss, oral and esophageal candidiasis, recent herpes zoster infection, anemia, leukopenia, H/C NA	CD4 26 VL 642,428 TDF, 3TC, EFV	Unmasking 4 wk	Umbilicated papules / nodules on face, no lymphadenopathy, no hepatomegaly, skin biopsy and culture +, H/C NA	CD4 147 VL-NA	Itra 400 mg/d x 4 wk, then 200 mg/d	At 3 wk: skin lesions completely resolved

Case Country, year reported, author	Age (yr), Sex	Status prior to starting ART Clinical, investigations	Immune status ART	IRIS type, Time to onset	Status at diagnosis of penicilliosis-associated IRIS Clinical, investigations	Immune status	Treatment	Outcome
9 China, 2015, Liu X et al. ¹⁷	47, M	Fever, molluscum contagiosum-like lesions, skin biopsy and H/C NA	CD4 32, VL-NA ART-NA	Unmasking 2 wk	Fever, rapid spread of skin lesions, leukopenia, thrombocytopenia, acute liver failure, CT: hypodense lesions in liver, intra-abdominal LN, skin biopsy and culture +, H/C +	CD4-NA VL-NA	AmphoB 0.8 MKD x 14 d, then Itra 400 mg/d	At 17 d: liver lesions resolved in CT scan At 1 mo: skin lesions completely resolved
10 USA (traveled to China), 2015, Iginosa O et al. ¹⁸	28, M	Fever, shortness of breath, chest x-ray compatible with PJP, H/C NA	CD4 10, VL-NA TDF, FTC, RPV	Unmasking 1 wk	Fever, headache, papules on face, trunk, extremities, skin biopsy and culture NA, H/C + on day 4	CD4-NA VL-NA	Methylprednisolone Liposomal amphotericin B 5 MKD x 2 wk, then Itra 400 mg/d x 10 wk, then 200 mg/d	Resolution of fever and rash
11 India, 2016, Nizami AI et al. ¹⁹	43, M	Fever, anorexia, weight loss, oral candidiasis, hepatosplenomegaly, anemia, H/C NA	CD4 10, VL-NA TDF, 3TC, LPV/r*	Unmasking 4 wk	Umbilicated skin lesions on face, no lymphadenopathy, skin biopsy and culture +	CD4 163 VL-NA	Itra 400 mg/d x 4 wk, then 200 mg/d	At 1 mo: skin lesions almost resolved
12 Vietnam, 2016, Thanh NT et al. ²⁰	31, F	Fever, weight loss, central necrotic nodules on face, body, oral ulcers, hepatosplenomegaly, pancytopenia, skin biopsy and culture +, H/C +, Rx Itra 400mg/d	CD4 10, VL-NA TDF, 3TC, EFV started 1 mo after resolution of fever and skin lesions	Paradoxical 5 mo	Fever, cervical lymphadenopathy, interphalangeal joint synovitis, dermatitis-like lesions on face, skin biopsy and culture -, H/C -	CD4 100 VL-NA	Itra 400 mg/d x 12 wk Ibuprofen for joint pain x 10 d	At 1 mo: complete resolution of symptoms
13 Vietnam, 2016, Thanh NT et al. ²⁰	35, M	Fever and skin lesions, skin biopsy and culture +, started Itra and currently on 200 mg/d	CD4 9, VL-NA TDF, 3TC, EFV	Paradoxical 3 mo	Scaly papules larger than before on face and trunk, lymphadenopathy, no fever, skin biopsy and culture +, H/C -	CD4 94 VL-NA	AmphoB 0.7 MKD x 14 d, then Itra 400 mg/d x 10 wk	At 1 mo: complete resolution of symptoms
14 Vietnam, 2016, Thanh NT et al. ²⁰	25, F	Fever, lymphadenopathy, central necrotic skin lesions, skin biopsy and culture +, Rx Itra 400 mg/d, fever and skin lesions resolved	CD4 2, VL-NA TDF, 3TC, EFV	Paradoxical 5 mo	Fever, new central necrotic skin lesions, purulent ulcers on both legs, interphalangeal joint synovitis, erythema nodosum, skin biopsy -, skin culture +, H/C -	CD4 96 VL-NA	AmphoB 0.7 MKD x 14 d, then Itra 400 mg/d x 10 wk Ibuprofen x 1 wk for joint pain	At 10 d: fever and skin lesions resolved Gradual clinical improvement over 3 mo
15 Thailand, 2017, Lee B, et al. (this case report)	16, M	Fever, anorexia, weight loss, no superficial lymphadenopathy / hepatosplenomegaly, complete blood count was normal, H/C -	CD4 71 VL=564,000 d4T, 3TC, EFV	Unmasking 1 wk	Fever, weight loss, jaundice, hepatosplenomegaly, peritonitis, no umbilicated skin lesions, anemia, leukopenia, CT: intra-abdominal lymphadenopathy, H/C +	CD4-NA VL-NA	AmphoB 0.7 MKD x 14 d, then Itra 400 mg/d x 10 wk, then Itra 200 mg/d x 6mo	At 6 wk: abdominal pain and fever resolved, weight gain At 3 mo: VL 330

Abbreviations: M, male; F, female; biopsy +, typical septate yeast cells seen; culture +, *Talaromyces marneffei* (formerly *Penicillium marneffei*) identified; H/C, hemoculture; d4T, stavudine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; ATV/r, atazanavir/ritonavir; RPV, rilpivirine; LPV/r, lopinavir/ritonavir; CD4, CD4 cell count (cells/mm³); VL, plasma HIV RNA level (copies/ml); NA, not available; LN, lymph node; PJP, *Pneumocystis jirovecii* pneumonia; MAC, *Mycobacterium avium* complex; AmphoB, amphotericin B deoxycholate; Itra, itraconazole; *2nd line ART

when a previously known OI recurs or becomes worse. Unmasking of IRIS manifests as a new OI which was previously inactive and unrecognized.

IRIS in adult Thai HIV-infected patients has been described in a study of 174 patients.⁵ The median pretreatment CD4 cell count was 37 cells/mm³. The median interval between starting ART and the onset of IRIS was 22 days. The incidence of IRIS in Thai patients was lower when compared to a meta-analysis of about 13,000 patients⁶ (6.3% vs. 13%), which may be due to delay of ART after diagnosing OIs. In the Thai study, IRIS was associated with tuberculosis, cryptococcal meningitis, and CMV retinitis.

The clinical manifestations and diagnostic methods of *T. marneffei* infection have been well described.^{7,8} Common clinical findings include fever (95%), weight loss (76%), skin lesions (71%), lymphadenopathy (57%), hepatomegaly (51%), cough (49%), diarrhea (31%), and splenomegaly (16%). Papules or nodules with central necrosis or umbilication may be seen on the face, trunk, and extremities. Investigations usually show anemia, leukocytosis and/or leukopenia, mild increases in serum bilirubin, aminotransferases, and alkaline phosphatase, and CD4 cell count < 100 cells/mm³. Presumptive diagnosis may be made before culture results become available by microscopic detection of yeast-like cells with a distinctive transverse central septum in Wright-stained samples of blood, bone marrow, or touch smears of skin or lymph node biopsies, as well as methanamine silver or periodic-acid Schiff-stained histopathological sections of skin lesions, lymph nodes, or bone marrow.

Over the past decade, only 14 cases of IRIS from *T. marneffei* infection have been previously reported worldwide⁹⁻²⁰ (Table 1). The mean pretreatment CD4 cell count was 25 cells/mm³. The mean interval between starting ART and the onset of IRIS was 7 weeks. Nearly all patients had umbilicated skin lesions; more than half had fever; one-third had superficial lymphadenopathy, hepatomegaly, arthritis / synovitis, or anemia; and one-fifth had splenomegaly or intra-abdominal lymphadenopathy. The majority of cases were unmasking of IRIS. In several cases, umbilicated skin lesions, which were mistaken for molluscum contagiosum, were not investigated.

The patient in the present case developed a very high fever, hepatosplenomegaly, lymphadenopathy, anemia, leukopenia, and transaminitis soon after ART initiation. The abrupt post-ART clinical deterioration in this severely immunocompromised patient had several differential diagnoses. First of all, drug toxicity was excluded. Efavirenz may cause Steven-Johnson syndrome (SJS), with is associated anemia and neutropenia, but the patient

did not have any cutaneous lesions consistent with SJS. The second possible cause was the clinical progression or presentation of previous OIs, such as disseminated tuberculosis, MAC, cryptococcosis, or CMV infection. However, there was no clinical or laboratory evidence of these OIs at the time of ART commencement. Also, there was no evidence of bacterial superinfection. Therefore, unmasking of IRIS was the most probable explanation. The patient likely had been harboring the pathogen prior to initiation of ART. He had low pretreatment CD4 cell count < 100 cells/mm³. The onset of symptoms was one week after starting ART, which showed a close temporal association, and was a possible time interval for IRIS occurrence. Unfortunately, HIV viral load and CD4 cell count at the time of the event were not available. However, a study has shown that HIV viral load and CD4 cell count should be used with caution in defining IRIS, as they did not always discriminate between IRIS from non-IRIS events, and were not included in the proposed revised case definitions for IRIS⁴, nor in the consensus case definitions for tuberculosis-associated and cryptococcal IRIS.^{21,22}

CONCLUSION

IRIS should be suspected in patients with low CD4 count who clinically worsen after starting ART. Clinical presentations of penicilliosis, with or without IRIS, are similar. However, with IRIS, manifestations may be more severe or atypical (arthritis, abdominal pain / mass). Umbilicated skin lesions should always be investigated and treated before initiating ART. Conventional antifungal treatment resulted in good outcomes in all 15 patients.

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