A child with swollen hands

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An 8 years old boy came to emergency department with painful swollen hands.

According to his uncle who brought him in, he has been well during the last 6 months after he moved into the family, except for “insect allergy” caused him off and on skin lesions at extremities.

Last week he started having a fever and decrease appetite.

Today he went fishing with his uncle until late in the afternoon.
Q#1 What is your first impression?

A. He might have insect bite/venom poisoning
B. It could be cellulitis at hands
C. He might have autoimmune disease
D. It might be a systemic infection involves skin and joints
E. Chronic arthritis from tuberculous infection is possible
• The boy has just moved into his uncle’s family after his mother died of unknown cause at another province, his father passed away years ago.
• The boy said that he has been smaller than other friends of his age since preschool class. He sometimes had pus from ears that resolved with medicine bought from drug store, but never been to any hospital during his living with mother.
• History of BCG and other vaccinations: no available document
• **Extremities:** Old impetigo scar (hypo- and hyper-pigmented areas), swollen hands, feet and elbows with warmness and tenderness

• **Chest:** normal equal breath sound, no adventitious sound

• **Abdomen:** liver 2cm below RCM, spleen not palpable.
Physical exam (2)

- **V/S**: BW 18 kg (5\textsuperscript{th}-10\textsuperscript{th} percentile), Ht 108 cm (<3\textsuperscript{rd} percentile), T 39.5\textdegree{}c, HR 130/min, RR 30/min, BP 100/60 mmHg

- **General appearance**: pale conjunctivae, fully conscious, well co-operated, enlarged lymph node at cervical and inguinal regions

- **HEENT**: small papular lesions on the face, some with central necrosis, pus in the Rt. ear canal, Thrush in mouth
Q#2 What labs/investigation would you plan to do first to get the diagnosis?

A. CBC, hemoculture, pus from ear for gram stain and culture
B. ESR, CRP, Anti-nuclear antibody, HIV antibody
C. CXR, tuberculin skin test, X-ray of affected parts
D. All of above
E. I want other investigations, not listed here.
Initial laboratory investigations: on admission

- CBC: Hb 7 g/dL, Hct 23%, WBC 3,640/mm$^3$ (N 76%, L 20%, Mono 1%), platelet count 145,000/mm$^3$
- Peripheral blood smear: normochromic normocytic RBC
- UA: WNL
- CXR: WNL
- Anti-HIV positive
- Tuberculin skin test: negative
- Stool exam: no RBC, WBC, no parasite
- ESR (60min): 110 mm
Initial laboratory investigations: on admission

X-ray of hands, feet and elbows
Summary of problems

1. History of fever for 7 days
2. Swollen hands, feet and elbows with warmth and tenderness (X-ray as shown)
3. Skin lesions at the face, PPE at extremities
4. Hepatomegaly
5. Chronic otitis media, oral thrush
6. Anti-HIV antibody positive
7. Pancytopenia
Q#4 What is the most likely opportunistic infection?

- A. Mycoplasma tuberculosis
- B. Cryptosporidiosis
- C. *Penicillium marneffei*
- D. *Herpes zoster*
- E. *Histoplasma capsulatum*
Skin scraping from a lesion at his face:

Wright stain
Distinguishing features of microorganism with similar size and stain properties

• **Histoplasma capsulatum:**
  – budding yeast cells

• **Penicillium marneffei:**
  – nonbudding yeast cells with characteristic central transverse septum
Bone lesion

- Osteolytic lesions at most phalanges (hands and toes)
**Penicillium marneffei**

- Penicillosis was the HIV-presenting illness in 25% in Vietnam.
- One of the most common opportunistic infection in northern Thailand
- Swollen fingers and/or toes was reported in 14% among 21 HIV-infected children with penicillosis

<table>
<thead>
<tr>
<th>Signs/symptoms (%)</th>
<th>Thai children(^1) (n=21)</th>
<th>Thai Adults(^2) (n=80)</th>
<th>India(^3) (n=36)</th>
<th>Hong Kong(^4) (n=47)</th>
<th>Vietnam(^5) (n=513)</th>
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<tbody>
<tr>
<td>Fever</td>
<td>100</td>
<td>93</td>
<td>97</td>
<td>96</td>
<td>82</td>
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<tr>
<td>Skin lesions</td>
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<td>71</td>
<td>81</td>
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<td>Anemia</td>
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<tr>
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<td>16</td>
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<tr>
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<tr>
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<td>presence of other OIs</td>
<td>43</td>
<td>55</td>
<td>77</td>
<td>57</td>
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</tbody>
</table>

Osteoarticular penicillosis

- It was not common, cases have been reported from China and Thailand.
- At CMU hospital during 1987-1991 there were 8 HIV-infected adults with bone and joint penicillium infection.
- Three of 8 presented with acute arthritis; all had clinical evidence of systemic penicillosis at the time of presentation.
- The ankle and wrist were the most commonly affected joint; osteomyelitis involved flat bones, long bone, and small bones of hands and feet were noted.
- Radiographic findings: osteolytic lesions with minimal sclerotic margin, without periosteal reaction (findings are not specific, and has to be differentiated from other granulomatous organism including Mycobacterium spp., or fungi)

**Penicillium marneffei**

- *P. Marneffei* is the only dimorphic fungus in the *Penicillium* genus.
- The first report in 1965 by Capponi et al. as a disease agent of the bamboo rat (*Rhizomys sinensis*) dying of disseminated mycosis in Vietnam; the strain was isolated at the Pasteur Institute in Paris.
- The first report of natural human infection in 1973 in an old missionary with Hodgkin’s lymphoma who had been living in Southeast Asia.
- Almost all cases were from many areas in Southeast Asia including Thailand, Southern China, Vietnam, Laos, Hong Kong, Taiwan, India.


Photo from: www.superstock.com
Q#4 What medication would you prescribe for this boy?

A. Fluconazole
B. Amphotericin B
C. Ketoconazole
D. Itraconazole
E. B and D
Preferred regimen for treatment of penicillosis

- Severe: Amphotericin B IV 0.7 mg/kg/day * 2 weeks then itraconazole 10 mg/kg/day oral bid *10 weeks
- Mild to moderate: itraconazole 10 mg/kg/day oral bid *8-10 weeks
- Secondary prophylaxis: itraconazole 5 mg/kg/day oral QD until immune recovery
- Response rate of 93% has been reported for the recommended amphotericin B/itraconazole regimen.

Course in the hospital

- Specific treatment:
  Amphotericin B IV for 5 weeks, then continued with itraconazole 10 MKD.

- Supportive and symptomatic treatment:
  Packed red blood cell transfusion.
  Ear toilet and ear drops.
Further Investigations

- **BM aspiration and smear:** The same organism as in the skin lesion smear was seen
- **Hemoculture:** *Penicillium marneffei*
- **BM culture:** *Penicillium marneffei*
Laboratory diagnosis of penicillosis

• **Cytological and histological examination**
  – Fine needle aspiration of lymph node, sputum cytology, touch/scrape smear of skin, peripheral blood smear

• **Microbiological culture**
  – The gold standard for diagnosis, time to positive 4 days (range 1.5-7)
  – Yield for culture: from bone marrow 100%, skin biopsy 90%, blood culture 76%

• **Serology and antigen testing**
  – Galactomannan assay (test developing for early detection of potential cases)

• **Molecular testing**
  – PCR assay (research setting)
Q#5 What is WHO clinical staging of this boy?

A. Stage 1
B. Stage 2
C. Stage 3
D. Stage 4
• An AIDS-defining illness listed in WHO stage 4
• The incidence of penicillosis increased rapidly with the development of HIV pandemic.
• The most frequent organs of involvement are liver and lungs, but skin, bone marrow, lymph node, and intestine can also be affected. Hemophagocytic syndrome has been reported.

*Penicillium marneffei*

His CD4 was 49 cells/mm³ (3%), and HIV RNA level >750,000 copies/mL

Q#6
When is the optimal timing for ART initiation?

A. Immediately at the same time with antifungal treatment
B. Delay until the end of first 2 weeks
C. Withheld for at least 4 weeks after infection subsided to avoid occurrence of IRS
D. Either A or B
Immune reconstitution syndrome (IRS) from penicillosis

- IRS is not a rare condition that could occur within a few weeks to months after potent ART initiation in patients with advanced stage HIV infection.

- Unusual manifestations of OIs could be seen with increasing CD4 cell count and/or decreasing HIV RNA level.

- In English literature review, between 2007-2011 there were 5 cases of IRS with disseminated *Penicillium marneffei* reported in adolescents and adults HIV-infected patients. Duration from ART initiation to IRS onset ranged between 2-8 weeks. Four of 5 successfully treated with Amphotericin B and itraconazole.

Q#7 What is your ART regimen of choice?

A. 3TC+ZDV+LPV/r
B. 3TC+d4T+NVP (or EFV)
C. 3TC+d4T+ Raltegravir
D. 3TC+ZDV+Maraviroc
Drug interaction between antifungals and antiretroviral agents

- **Itraconazole**: inhibit metabolism of CYP3A4 substrates
  - Increase plasma concentration of PIs (IDV, RTV, SQV) and vice versa.
  - Increase concentration of maraviroc

- **NNRTIs** reduce itraconazole concentration by promoting its metabolism

- In general no significant interaction with most NRTIs and integrase inhibitors.
• The fever persisted for 5 weeks, then gradually subsided.

• He was given IV amphotericin B for 6 weeks, then followed by itraconazole orally.

• Lastavir (3TC/d4T) + EFV was started at the end of the first week in hospital ward

• His swollen hands, elbows and feet also gradually disappeared.

• The boy was discharged home with itraconazole 10 MKD
Take home message

• *Penicillium marneffei* is an opportunistic pathogen which became an AIDS-defining illness in the endemic areas.

• Most patients present with constitutional symptoms; skin lesions, anemia, lymphadenopathy, respiratory symptoms, and osteoarticular involvement could be seen

• Prompt diagnosis: skin smear for wright’s stain

• Standard antifungal regimen: amphotericin B follows by maintenance with itraconazole

• Secondary prophylaxis: after completed treatment until after immune restoration (CD4 cell count > 100 cells/mm³ for over 6 months)