Case 8

A 50 year-old Thai female from Chonburi province

Chief complaint: Prolong fever for 5 months

Present illness: The patient presented with prolonged fever, generalized lymphadenopathy and chronic productive cough for 5 months. She went to a primary care hospital and was diagnosed as pneumonia and subacute lymphadenitis from supraclavicular lymph node biopsy. She was treated by a course of antibiotic treatment without any improvement.

Two weeks ago, she developed multiple discrete erythematous papules and pustules on face, trunk and extremities. She was treated with topical corticosteroids and oral antihistamine. The rash was resolved but subsequently recurred. She still had fever, loss of appetite and loses weight from 53 kg to 45 kg in 3 months

Underlying disease: She had no underlying disease. She had history of allergic skin rash to Ibuprofen.

Family history: There was no family history of TB or similar lesion.

Dermatologic examination:

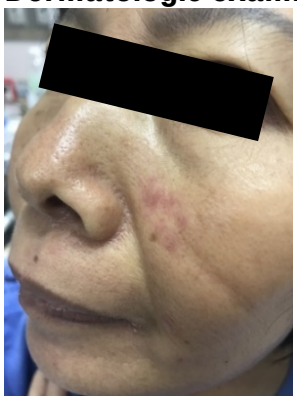

Fig. 8.1

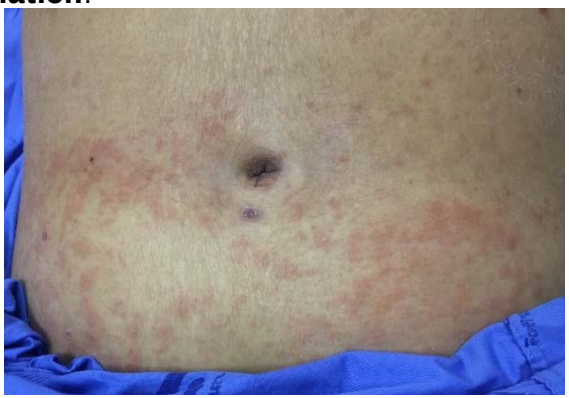

Fig. 8.2

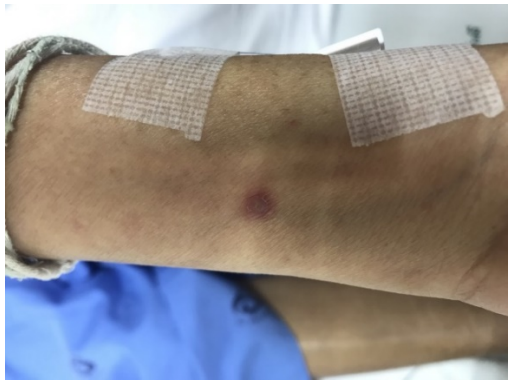

Fig. 8.3

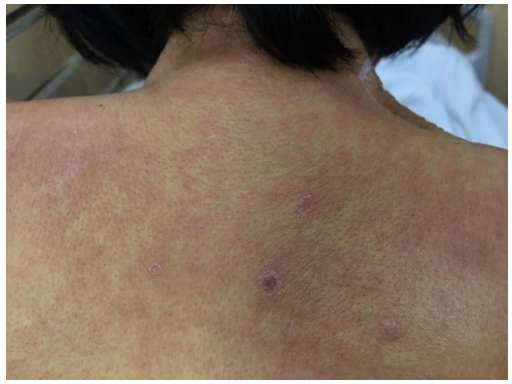

Fig. 8.4

-Solitary erythematous papule with crusted erosion on the center on left cheek. (Fig. 8.1)

-Multiple discrete blanchable erythematous macules, papules and pustules some coalescing into plaques on face, trunk, forearms and both legs. (Fig. 8.2, Fig. 8.3, Fig. 8.4)

Physical examination:

V/S: BT 38 ^{O}C, PR 100 bpm, RR 20 times/min, BP 100/60 mmHg
HEENT: moderately pale conjunctivae, no mucosal lesions
Lymph node: lymphadenopathy at bilateral supraclavicular, cervical, right inguinal lymph node
Lungs: decreased breath sound LLL
Other examinations were within normal limits.

Lab investigations:

- **CBC**
  - WBC 27,680/mm^3 (N 75, L 14, M 1, Eo 6, B 4%)
  - Hb 7.2 g/dL Hct 24.2 %, MCV 89 fL
  - Plt 551,000/mm^3
- **Liver function test:** AST/ALT 26/28 U/L, ALP/GGT

514/350 U/L, TP/Alb 73/18 g/L, TB/DB 0.7/0.5 mg/dL

- **Renal function:** BUN/Cr 8/0.63 mg/dL
- **Anti-HIV:** negative
- **CXR:** linear and hazy opacity at left middle-left lower lung zone could be left pleural effusion with passive LLL atelectasis.
- **CT chest with whole abdomen:**
  - Moderate left pleural effusion with atelectasis of the LLL and lingual, mass- like consolidation at superior lingual, multiple small (2-4 mm) non-calcified solid pulmonary nodules in both upper lobes and RML.
  - Multiple lymph node enlargement (bilateral axillary, subpectoralis regions, bilateral inguinal, right common iliac, bilateral external iliac, paraaortic regions, periportal region)
  - Mild hepatomegaly. A 0.4-cm hypodense lesion at segment VII.
- **Left cervical lymph node for 18s**: *Histoplasma (Ajellomyces) capsulatum*, culture: *Mycobacterium abscessus*
- **Skin biopsy for 18s:** *Histoplasma (Ajellomyces) capsulatum*
- **Skin culture for fungus:** 2/4 *Histoplasma (Ajellomyces) capsulatum*
- **Liver biopsy culture:** *Mycobacterium avium complex*
- **Pleural tapping culture:** *Mycobacterium avium complex*
- **Bronchoalveolar lavage culture:** *Mycobacterium avium complex*
- **Bone marrow biopsy culture:** *Mycobacterium avium complex*
- **Hemoculture:** *Mycobacterium avium complex*
- **Anti-interferon (IFN)-γ antibody**: positive

Histopathology: (S18-013393, skin, right abdomen)

(Fig. 8.5, Fig. 8.6)

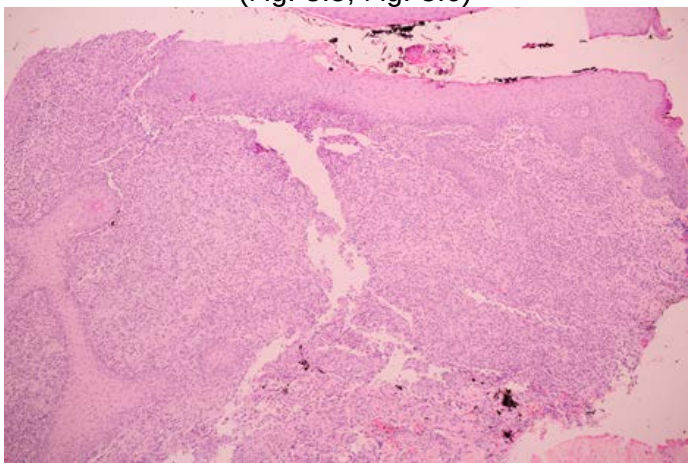

Fig. 8.5

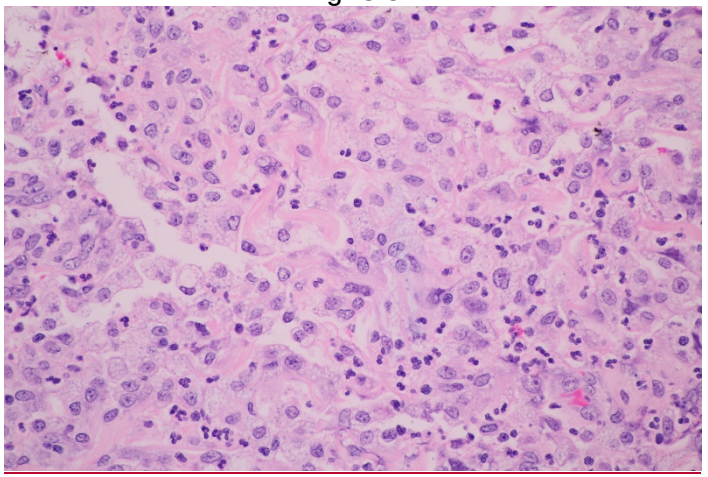

Fig. 8.6

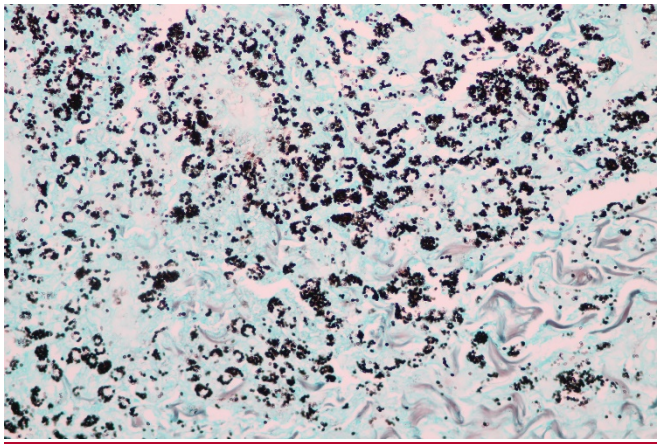

Fig. 8.7

- Diffuse inflammatory cells infiltration composed of lymphocytes, histiocytes and neutrophils in the upper to deep dermis (Fig. 8.5)
- Pseudocarcinomatous epidermal hyperplasia (Fig. 8.5)
- Round to oval fungal element 2-4 micromillimeter within the cytoplasm of histiocytes (Fig. 8.6)
- Positive GMS (Fig. 8.7)

Diagnosis: Disseminated Histoplasmosis infection with co-infection (disseminated Mycobacterial abscessus, disseminated MAC) in an anti-IFN-γ autoantibody patient

Treatment

- Disseminated Histoplasmosis: intravenous amphotericin B 0.9 mg/kg/day for 2 weeks and then switch to 3 months oral itraconazole 400 mg once daily for antifungal prevention.
- Disseminated MAC, NTM: intravenous Imipenam 500 mg every 8 hrs, intravenous levofloxacin 750 mg od, oral Clarithromycin 500 mg twice a day for 2 weeks, then add oral ethambutol 800 mg once a day when disseminated MAC was diagnosed. After treatment intravenous imipenam and levofloxacin complete 2 weeks then change to oral clarithromycin 500 mg twice a day, oral ciprofloxacin 500 mg, oral etambutol 800 mg at least 1 year.
- Anti-IFN-γ autoantibody: intravenous rituximab 500 mg 2 doses, pulse methylprednisolone 1 g/day intravenous for 3 days.

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Discussion:

In patient with disseminated histoplasmosis infection with co-infection (disseminated Mycobacterial abscessus, disseminated MAC) can occur in immunocompromised patient particularly in HIV patient who has low CD4. However in this patient was anti-HIV negative, so others acquired immunodeficiency that defective T-cell such as autoantibody to interferon- γ should be considered.[1]

Autoantibody to interferon gamma has been first reported in Thailand on 2000 and continue to increase of reports about the adult onset immunodeficiency .[2,3] It has been founded 88% of Asian adults with multiple opportunistic infection.[2] Because anti interferon-γ autoantibodies block interferon γ activation and then restrain interferon-γ and interleukin-12 pathway, Trigger for production of these autoantibodies remains unknow.[2] Anti–IFN-γ autoantibodies may be a critical role in the pathogenesis of NTM infection and reactivation of latent varicella-zoster virus infection and are associated with genetic factors (HLA-DRB1*16:02 and DQB1*05:02) but we need further investigation for determine the specific HLA alleles and induce anti-IFN-γ autoantibodies production

[4]. Anti–IFN-γ autoantibodies increases risk of intracellular infection such as nontuberculous mycobacteria, dimorphic molds (*Histoplasma capsulatum*, *Cryptococcus neoformans*, *Pennicillium marneffei*), nontyphoidal *Salmonella* spp, *Burkholderia* spp, severe varicella-zoster virus. [2] The prognosis of anti-IFN-γ autoantibodies is 32% mortality by a median of 25 months after diagnosis.[3]

Common cutaneous presentations of anti-IFN-γ antoantibodies include sweet syndrome, pustular psoriasis, acute generalized exanthematous pustulosis, erythema nodosum and others.[5] In this patient who presented with solitary erythematous papule with crusted erosion on the center on left cheek and multiple discrete blanchable well-defined erythematous macules, papules and pustules some coalescing into plaques on face, trunk, forearms and both legs. Skin biopsy from right abdomen and left cervical lymph node biopsy showed *histoplasma capsulatum*

Histoplasmosis is also called Darling's disease. It is a deep mycotic infection devided into 2 species. *Histoplasma capsulatum* is found in the Americas and the tropics, especially the Ohio and Mississippi river valleys of North America.[6] *Histoplasma dubosii* is found in Africa.[7] It is a dimorphic fungus affecting the reticuloendothelial system.[7] Transmission by inhalation of conardia from the environment. The spore are found in soil, bird and bat dropping.[8,9] It presented with many manifestations, with pulmonary involvement being the most common[9] and disseminated histoplasmosis can involving the skin lesions.

Mucocutaneous manifestation may be primary(very rare) and caused by direct inoculation or secondary due to hematogenous spread. The primary cutaneous lesion may appear as an ulcer or a painless chancre with regional lymphadenopathy and usually appears in weeks or months. Skin lesions are not specific and can be papules, plaques with or without crusts, pustules, nodules. It can be umbilicated lesions resembling molluscum contagiosum, acneiform eruptions, erythematous papules with keratotic plaques, purpuric lesions, and localized and generalized vegetant forms of dermatitis.[10, 11] Oral lesions can be painful skin colored papules and nodules with erosion or ulcer[1] on tongue, gums and larynx[10] and may be affected in 75% of patient. The most common sites are face, extremities, trunk, oral, perianal and genital mucosa.[10, 11]

The direct microscopic examination with Wright's or giemsa stain show intracellular yeasts.The histopathology is recommended because it can be diverse morphologic presentations of the pathologic fungus. The special stain such as periodic acid-Schiff (PAS), silver methenamine, or Gomori-Grocott stains can be helpful.[12] The histopathology shows granulomas, with or without caseous necrosis, lymphohistiocytic infiltrates and presence of fungus in form of yeast[12]. The culture in Sabouraud's glucose agar following incubation at following incubation at 25°C is the gold standard but it takes long times about 6-12 weeks.[13] 18S rRNA is early detection in 24 to 48 hours and can be a useful additional tool for diagnosis of *Histoplasma Capsulatum,* especially in non-endemic regions.[13] Same as this patient, the histopathology shows lymphocytes, histiocytes and round to oval fungal element within the cytoplasm of histiocytes. Moreover, GMS, PMS, 18s rRNA are positive.

Treatment for Histoplasmosis requires an induction phase and maintenance phase. Antifungals include azole groups and Amphotericin B. Induction therapy for moderate-severe disseminated histoplasmosis patient uses amphotericin B dose 0.7

to 1 mg/kg daily for 12 weeks[14] and second option is itraconazole for patient in mildly or moderately ill. The loading dose is 200 mg 3 times daily for 3 days, then maintenance doses of 200 mg once or twice daily. Maintenance therapy may be lifelong, using itraconazole 200 mg once or twice daily.[14]

In this patient, intravenous amphotericin B 0.9 mg/kg/day for 2 weeks and then switch to oral itraconazole 400 mg daily for treat disseminated histoplasmosis. intravenous imipenam 500 mg every 8 hrs, intravenous levofloxacin 750 mg od, oral Clarithromycin 500 mg twice a day for 2 weeks, then add oral ethambutol 800 mg once a day when disseminated MAC was diagnosed. After treatment intravenous imipenam and levofloxacin complete 2 weeks then change to oral clarithromycin 500 mg twice a day, oral ciprofloxacin 500 mg, oral etambutol 800 mg at least 1 year for treat disseminated MAC, NTM. And intravenous rituximab 500 mg 2 doses, pulse methylprednisolone 1 g/day intravenous for 3 days for treat anti-IFN-γ autoantibody. There were reported case treated with rituximab in severe infection[15] or rituximab combined with methylprednisolone.[16]

After treatment for 2 months, the lesions were improved but at 2 weeks later, she developed multistage group of vesicles on face, trunk and extremities. Tzanck smear was show acantholytic cell and multinucleated cell. She was diagnosed as varicella infection and referred to nearby hospital for acyclovir 500 mg intravenous every 8 hours for 7 days. Unfortunately, she passed away from septic shock with *Staphylococcus aureus MRSA*, *Klebsiella pneumoniae pneumonia* and *staphylococcus epidermidis* septicemia. Hemoculture for fungus was not report in this time.

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