Important Decisions in Dermatopathology

Cases in Dermatologic Infectious Disease

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Case #1

- 38 yo woman presented with new-onset, painful, multiple firm nodules on her hands, wrists, and posterior legs that had been growing in size and number over the previous several weeks.

- She has common variable immunodeficiency (CVID) and hepatic cirrhosis of probable autoimmune etiology.

- Her medications at the time included intravenous immune globulin (IVIG), prednisone (10mg per day), and azathioprine (75mg per day).
Subcutaneous nodule under the PIP joint
Subcutaneous nodule on the wrist
A biopsy was performed of the nodule on the PIP joint...
This process is most likely associated with which Mycobacterial infection:

1. *M. tuberculosis*
2. *M. marinum*
3. *M. chelonae*
4. *M. haemophilum*
Mycobacterium haemophilum

M. haemophilum is a nontuberculous mycobacterial infection that can affect the skin, joints, bone, and lungs of immunocompromised patients (usually HIV or transplant).

Skin lesions, such as papules, nodules, or plaques, are the most common presenting symptom and often occur over joints.
Differential Diagnosis

- Differential diagnosis of AFB positive organisms within cutaneous granulomas:
  - *M. haemophilum*
  - *M. chelonae, M. fortuitum, and M. abscessus*
    - Usually ulcers or subQ nodules
    - Lesions tend to be multiple and may lead to draining fistulas
    - Causes: immunosuppression +/- trauma or injection
    - Other organs involved in disseminated disease: eye, lung, heart
  - *M. gordonae*
    - Rare and usually associated with severe immunosuppression
    - More commonly causes severe lung disease in HIV patients
    - Skin nodules may develop following soil exposure or trauma in healthy patients or dissemination in immunocompromised patients
Differential Diagnosis

Differential diagnosis of AFB positive organisms within cutaneous granulomas:

- **M. kansasii**
  - Most commonly causes a lung infection similar to tuberculosis
  - Skin lesions may resemble sporotrichosis with ulcers or nodules and lymphatic spread
  - Disseminated disease is more common in severe HIV infection

- **M. marinum**
  - Infection follows exposure of open skin to nonchlorinated water
  - Papule or ulcer is present at the site of involvement, and lymphatic spread often occurs
  - May involve underlying joint

- **M. tuberculosis**
**Histologic findings of M. haemophilum**

- **Granulomas**
  - Caseating or non-caseating granulomas in the dermis and/or subcutaneous tissue
  - AFB organisms may be present
  - Patients with CVID often develop well-formed granulomas
  - AIDS patients may show poorly formed granulomas

- **Interstitial histiocytic infiltrate**
Well formed dermal granuloma with central necrosis and peripheral palisading
AFB positive organisms associated with the granulomas
AFB positive organisms associated with the granulomas
A 47-year-old woman with myasthenia gravis, status post thymectomy, presented with a one year history of painful, erythematous papules and indurated nodules on her arms, hands, and lower extremities.

Her medications at the time included pyridostigmine, prednisone (30mg and 5mg on alternating days), azathioprine, and mycophenolate mofetil.
Ill-defined erythematous to violaceous plaques on the legs
**M. haemophilum Histologic Spectrum**

- Mixed dermal infiltrate, with prominent interstitial granulomatous dermatitis.
- Periodic-acid Schiff and acid-fast staining did not initially reveal the presence of organisms, although a subsequent biopsy at the site of another active lesion showed acid-fast organisms.
- Culture grew *M. haemophilum*
Interstitial lymphohistiocytic infiltrate in the dermis
Case #2

- 49-year-old white male presented in August 2006 with a 4 month history of an enlarging non-healing ulcer on his right shin.
- He also noted two smaller lesions on his lower leg in addition to some unilateral swelling.
- Bacitracin and hydrogen peroxide produced minimal improvement.
Case #2

- **Past medical history:** $\alpha_1$-antitrypsin deficiency treated with a bilateral lung transplant in 1995.
- **Social history:** He is a contractor and is frequently exposed to trauma in his lower extremities.
- **Medications:** tacrolimus, prednisone (10 mg QD), allopurinol, trimethoprim/sulfamethoxazole, valganciclovir
Case #2

Physical Examination:

- On initial presentation in August, there was a 3 x 2 cm ulcer with an indurated border present on the patient’s right anterior lower leg.
- Two erythematous nodules were noted in close proximity, one with minimal ulceration.
- His right lower leg revealed pitting edema.
- In addition, moon facies, truncal obesity, and atrophic, purpuric skin (on his forearms) were present.
Indurated ulcerations on the left lower leg
The most likely infectious cause of this patient’s ulcerations is:

1. Chromoblastomycosis
2. Sporotrichosis
3. Hyalohyphomycosis
4. Phaeohyphomycosis
Phaeohyphomycosis
**Phaeohyphomycosis**

- Biopsy results from this patient are consistent with phaeohyphomycosis; however, cultures were also performed for definitive speciation.
- Due to the possibility of drug interactions, we worked with the transplant team to initiate appropriate therapy.
- Patient was started on Itraconazole 200 mg QD and has had good results.
Phaeohyphomycosis

- Culture from the wound bed of the large ulcer demonstrated a dematiaceous (pigmented) fungus.
- Further mold identification implicated an *Exophiala* genus.
- Ribosomal DNA sequencing identified our isolate as *Exophiala spinifera* by comparison with the Centraalbureau voor Schimmelcultures database at the Royal Netherlands Academy of Arts and Sciences.
**Phaeohyphomycosis**

Dematiaceous (pigmented) fungi can cause:

- **Phaeohyphomycosis**: invasive, usually cutaneous, disease characterized by pigmented septate hyphae in culture and tissue

- **Chromoblastomycosis**: superficial cutaneous disease presenting with nodules or verrucous masses and characterized by pigmented, round, sclerotic bodies

- **Mycetoma**: chronic cutaneous infection characterized by draining sinuses and the presence of granules within the exudate
Phaeohyphomycosis

- Agents that cause this infection are primarily soil saprophytes, plant pathogens, and contaminants in the environment.
- > 100 species belonging to at least 57 genera are known to cause phaeohyphomycosis.
- Frequent causes of human infection include: *Exophiala, Wangiella, Bipolaris, Curvularia, Exserohilum, and Alternaria*. 
Phaeohyphomycosis

- Occurs primarily in immunocompromised hosts, with many reports in transplant patients.
- Most transplant patients are on 2 or more of the following drugs when the disease occurs: prednisone, tacrolimus, and mycophenolate mofetil.
- Usually causes cutaneous disease, with rare occurrence of dissemination.
Phaeohyphomycosis

- Lesions typically evolve from primary inoculation at a site of minor trauma contaminated with plant materials.
- Begins as a small erythematous and indurated papule which may progress to an ulceration or nodule.
- Cutaneous disease may exist as multiple lesions and can persist for months or years.
- Dissemination, a rare, life-threatening complication, occurs primarily in the immunocompromised host and may involve many organs, including the central nervous and cardiovascular systems.
Phaeohyphomycosis

- Diagnosis is made through demonstration of the brown pigmented fungus on histopathologic examination and culture.
- The pigmented hyphae within tissue demonstrate thick septations and prominent constrictions.
- Further mold identification may be carried out using Ribosomal DNA sequencing.
Granulomatous and neutrophilic infiltrate

Prominent pseudoepitheliomatous hyperplasia

Granulomatous and neutrophilic infiltrate
Granulomatous and neutrophilic infiltrate
GMS stain showing hyphae within the tissue demonstrate thick septations and prominent constrictions.
Pigmented fungal hyphal elements are noted on routine H+E staining, and melanin pigment is highlighted using a Fontana-
Other Cases in Transplant Patients
Patient 1:
- 65 year old female
- Cardiac transplant 2 years prior
- Medications: Azathioprine, prednisone, cyclosporine
- Presents with 6 week history of an ulcerative lesion on the finger
- One month later, a nodule appeared close to the initial lesion and excision was performed
Two cases of subcutaneous phaeohyphomycosis due to *Exophiala jeansiemi*, in cardiac transplant and renal transplant patients

![Image 1](image1.png)

**Figure 1.** (A) Initial cutaneous ulcer on the flexor side of the proximal phalanx of the left index finger. (B) Subcutaneous lesion on the flexor side of the proximal phalanx of the left index finger. This ulceration appeared 1 month after the initial lesion.
Two cases of subcutaneous phaeohyphomycosis due to *Exophiala jeaneselmei*, in cardiac transplant and renal transplant patients

Figure 2. Photomicrograph showing granulomatous inflammation and numerous branching fungal hyphae (arrows) (periodic acid-Schiff; original magnification ×100).
• Cultures grew *Exophiala jeanselmei*

• Only topical “antiseptics” were prescribed and the lesions resolved

• 15 months later, a third lesion appeared one centimeter from the initial lesion

• Spontaneous healing was again observed and no antifungals were given

• Patient has been clear for 6 years
57 year old with IDDM
Heart transplant one year prior
Medications: prednisolone, azathioprine, tacrolimus
Surgical excision for “atheroma” on the shoulder
- No history of trauma
- Cultures grew out *Bacteroides fragilis* x 2
- Histology showed no evidence of fungi
Wound healing was impaired over the next 2 months, and wound edges became pigmented.
Two months after the excision, the patient developed nausea, singultus (hiccups), and ataxia.
Culture of the cutaneous wound edges demonstrated a dematiaceous black mold, *Cladophialophora bantiana*. Biopsy and culture of the cerebellar lesion showed the same organism. Despite appropriate treatment and close monitoring of itraconazole peaks/troughs, the patient expired one month later from sepsis.
Phaeohyphomycosis is an invasive, usually cutaneous, disease characterized by pigmented septate hyphae. Many organisms can cause this infection, and they are primarily soil saprophytes or contaminants in the environment. Usually present in immunocompromised patients with a history of cutaneous trauma. Diagnosis through histology and culture. Treatment most commonly local excision or itraconazole.
Case #3

- A 49 year-old woman with rheumatoid arthritis (RA) presented with a severely swollen right fourth finger associated with fissuring and crusting.
- Multiple firm pink papules and deeper subcutaneous nodules were present on the dorsal hand and extended proximally along the forearm.
- Nine months prior to presentation, she developed small papules overlying the fourth digit, with associated joint pain, after suffering from a minor laceration in the area.
Case #3

- The patient has long-standing RA, for which she takes methotrexate, infliximab, and sulfasalazine.
- Initially, her joint symptoms were attributed to her RA, and she continued her immunosuppressive therapy.
- Her condition progressed with increasing joint pain, edema, and new papules and nodules.
- An MRI revealed a joint effusion and findings suggestive of tenosynovitis.
- Surgical debridement demonstrated necrosis and granulomatous inflammation within the joint space.
Severely swollen right fourth finger associated with fissuring and crusting.
Multiple firm pink papules and deeper subcutaneous nodules extended proximally along the forearm.
Biopsy of the initial lesion from the finger
Biopsy from a nodule on the wrist
This process is most likely associated with which *Mycobacterial* infection:

1. *M. tuberculosis*
2. *M. marinum*
3. *M. chelonae*
4. *M. fortuitum*
Mycobacterium marinum

Disease Course

- Acid-fast bacilli were present within the granulomas.
- Tissue cultures from both biopsy sites grew *Mycobacterium marinum*.
- The patient was treated with azithromycin, ethambutol, and trimethoprim/sulfamethoxazole, and her methotrexate and infliximab were discontinued.
- After six months of treatment, the patient had significant improvement; however, the severity of the initial infection resulted in significant functional impairment of the finger.
Mycobacterium marinum

- *M. marinum* is a non-tuberculous mycobacterial infection that typically occurs on the hand or upper extremity following minor trauma and exposure to water or marine animals.
- The patient had a fresh-water fish tank.
- The infection may begin as a papule, nodule, or ulcer within weeks to months of inoculation.
- As the infection progresses, multiple nodules may develop in an ascending fashion along the path of lymphatic drainage.
- *M. marinum* infection may be suggested by history and routine histopathology, but confirmed with tissue culture.
**Mycobacterium marinum**

- *M. marinum* infection may remit spontaneously; however, some cases progress to cause tenosynovitis, septic arthritis, osteomyelitis, or disseminated disease without proper treatment.

- Immunosuppression is a significant risk factor for severe infection with *M. marinum*.

- In one series of 35 patients with invasive *M. marinum* infection, 40% had a steroid injection at the site of infection, 26% were taking systemic steroids, and 11% were immunocompromised from other causes, such as chemotherapy or AIDS.
Biopsy of the initial lesion from the finger:

- Overlying lichenoid inflammation
- Deep granulomatous panniculitis
Deep granulomatous inflammation
Biopsy from a nodule on the wrist

Well-formed granulomas with central necrosis
Well-formed granulomas with central necrosis
Infections included 16 cases with *M. marinum*, 3 of atypical *Mycobacterium* without species identification, and one each with *M. chelonae*, *M. xenopi*, *M. abscessus*, *M. gordonae*, and *M. fortuitum*.

Most of the cutaneous lesions were located on the UE (74%), especially the fingers (59%).

Sporotrichoid distribution was present in 33% of cases.

The clinical appearance of the lesions was variable and included nodules, papules, plaques, ulcers, and cyst.

A history of trauma preceded the lesions in 10 patients (44%).
Histologic patterns

Granulomas were present in 9 specimens (37.5%) and acid-fast bacilli were identified using Ziehl-Neelsen stains in 3 of 18 specimens (16.7%).

The mean duration of the skin lesions in which biopsy specimen revealed granulomas (7.9 months) was longer than in the nongranuloma group (4.7 months).

Histologic changes in the epidermis differed in each case and included features such as acanthosis, pseudoepitheliomatous hyperplasia, and ulceration.
Different histopathologic patterns in cutaneous NTM infections

- A granulomatous inflammatory infiltrate with tuberculoid granuloma formation, sarcoid-like granulomas, or rheumatoid-like nodules are frequently present.
- Other findings described include dermal or subcutaneous abscesses, a diffuse dermal or subcutaneous histiocytic infiltration, acute or chronic subcutaneous tissue inflammatory infiltrates (panniculitis), or nonspecific chronic inflammation.
- The histologic findings in this study revealed lower % of granuloma and staining for AFB organisms in the biopsy specimens than previously reported.
- These results may be explained in part by the fact that a large portion of our patients had early stages of *M. marinum* skin infection in which the histology usually demonstrates nonspecific inflammation.
Nontuberculous mycobacterial infections of the skin: A retrospective study of 25 cases

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- Because there is no pathognomonic clinical picture and the histologic findings vary, a skin biopsy specimen is recommended for culture in addition to histology.
- PCR is a rapid, sensitive, & specific diagnostic tool.