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Gram-negative Cutaneous Infections with Unique Filamentous Forms

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In the setting of acute infection in a neutropenic patient, often heralded by a cutaneous eschar or retiform purpura, prompt diagnosis is of utmost importance. Although tissue culture is most commonly used for speciation, hematoxylin and eosin (H&E) can be helpful in identifying the morphology of the infectious organism, especially in those cases where mycology cultures can take days to weeks.

Herein we highlight a diagnostic challenge that may lead to discordance between Gram stain and tissue culture identification. Filamentation is a bacterial response in the setting of antimicrobial therapy, particularly beta-lactam antibiotics, whereby bacteria replicate but incompletely divide.^{1,2} This can result in the formation of long slender chains that resemble fungal hyphae.³ Filamentation has primarily been described *in vitro*^{4–6} and within direct cytology smears of body fluids^{3,7}, leading to misdiagnosis.³

Bacterial filamentation appears to be an uncommon finding in cutaneous pathology. We describe two patients who developed Gram-negative bacterial infections that showed filamentous forms on H&E and/or Gram stain. In both cases, the patients had received antecedent systemic antibiotics and multiple biopsies for tissue culture were performed to confirm the diagnosis.

The first patient was a 56-year-old female with multiple myeloma and a history of an autologous and T-cell depleted allogeneic hematopoietic stem cell transplant who presented with cellulitis on the nose. The patient had recently been admitted twice for recurrent neutropenic fevers in the setting of herpetic stomatitis and pan-sinusitis. The night prior to admission, she reported expressing keratinaceous debris from a pimple on her nose with a metal comedone extractor. Subsequently, the area became tender and inflamed, and on physical exam the patient had a one-centimeter purpuric patch involving the tip of her nose (Figure 1A). Biopsy and tissue culture were obtained four hours after the patient received empiric vancomycin and piperacillin-tazobactam. Despite tissue culture growing abundant *Pseudomonas aeruginosa* (a Gram-negative bacterium that is typically rod shaped), Gram-negative filamentous structures, admixed with some smaller bacilli, were observed on Gram stain (Figure 1C–1E). PAS and Fite stains were negative. A second tissue culture of the site three days later also grew *Pseudomonas aeruginosa*. The patient's infection resolved with cefepime and the residual eschar continued to heal with local wound care (Figure 1B).

The second patient was a 44-year-old male with a history of left testicular nonseminomatous germ cell tumor and autologous hematopoietic stem cell transplant who was admitted with neutropenic fevers and empirically treated for six days with vancomycin and piperacillin-tazobactam. Dermatology was consulted to evaluate three days of tender axillary swelling and erythema. On physical exam, the patient had multiple subcutaneous nodules in the bilateral axillae (Figure 2A). A skin biopsy revealed filamentous forms of bacteria amidst a background of granulomatous inflammation intermixed with nearby remnants of a ruptured follicle and associated fibrinous necrosis. (Figure 2B–2D) While there was initial concern for *Nocardia* or *Actinomyces*, the tissue culture grew *Klebsiella pneumoniae*. PAS and Fite stains were negative. Subsequently, a second tissue culture from the contralateral axilla also grew *Klebsiella pneumoniae*, and the patient later had blood cultures positive for *Klebsiella pneumoniae* bacteremia. The infection resolved with meropenem and ciprofloxacin.

Post-antibiotic filamentation of Gram-negative bacilli in the context of cutaneous histopathology is noteworthy. This phenomenon has previously been described in direct cytology smears of body fluids. Sutton et al³ reported two cases of *Escherichia coli* adopting a filamentous morphology, both having been initially misdiagnosed as fungal hyphae. The first patient was a young girl with *E. coli* meningitis and filamentation on cerebrospinal fluid Gram staining; the second patient was an elderly woman with *E. coli* urinary tract infection and filamentation on urine Gram staining. Suwantar et al⁷ described a 21-year-old African-American female with a history of sickle cell anemia who presented with fever and back pain; Gram stain of blood culture medium showed *Klebsiella pneumoniae* filamentous forms in the presence of sub-inhibitory concentrations of β -lactams.

Furthermore, literature has documented filamentation of Gram-negative rods *in vitro*. Lorian et al⁴ described filamentation of *E. coli* when incubated with either ciprofloxacin or ampicillin, and this occurred as soon as one hour after antibiotic exposure. Diver et al⁵ also described extensive filamentation of *E. coli* after exposure to ciprofloxacin at levels close to the minimum inhibitory concentration. Klein et al⁶ demonstrated filamentation of *Haemophilus influenzae* when incubated with inhibitory levels of ampicillin, and extensive

filamentation was observed following four hours in the presence of antimicrobial therapy, a timeframe comparable to our first patient.

Studies have postulated that bacterial filamentation may be a survival mechanism.^{1,8} First, the dramatic increase in size (sometimes reaching lengths of at least 50 times an ordinary bacillus) might allow for the evasion of neutrophil phagocytosis. Second, as this process is facilitated by incomplete cell division, filamentation may be protective against the lethal effects of cell wall destruction mediated by antibiotics.

Filamentation of Gram-negative rods should be considered in the differential diagnosis of filamentous forms visualized on H&E. Here we highlight two Gram-negative rods, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, that can exhibit filamentous forms in cutaneous histopathology. Without knowledge of this phenomenon, the specimen may be misdiagnosed as fungal hyphae, *Nocardia*, *Actinomyces*, or another infectious pathogen. It is important to note however that even though filamentous forms of bacteria can mimic fungi, morphologically they are thinner in diameter and aseptate.

Overall, this information must be considered in the context of the patient's profile, response to treatment, and ancillary studies. If the diagnosis remains in question, additional tissue samples for culture can be helpful in providing further diagnostic data.

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Figure 1:

Patient 1.

A) Purpuric patch at nasal tip

B) Purpuric patch has now evolved into eschar

C) Hematoxylin and eosin stain, 40X, highlights the dermal infiltration of mixed inflammatory cells

D) Hematoxylin and eosin stain, 1000X; Rod-shaped filamentous forms are seen in high power.

E) Gram Stain, 1000X; Gram-negative filamentous forms, ranging in size from 5 to 20 micrometers are highlighted.

Figure 2:

Patient 2.

A) Subcutaneous nodules in the right axilla

B) 20X, Hematoxylin and eosin stain: superficial and deep dermal mixed inflammatory infiltrate

C) 1000X; Hematoxylin and eosin stain, highlights the rod shaped filamentous forms

D) Gram stain, 1000X; Gram-negative filamentous forms, ranging in size from 10 to 30 micrometers.