

Extraintestinal Involvements of Crohn's Disease Complicated with *Nocardia* Bacterium: An Overview Due to A Case

Onur Özgenç^{1*}, Seher Ayten Coşkuner², Hakan Evren³, Meltem Avci²

¹Dokuz Eylül University Vocational School of Health, Izmir, Turkey

²Department of Infectious Diseases and Clinical Microbiology, Izmir Bozyaka Teaching and Research Hospital, Izmir, Turkey

³Department of Infectious Diseases, Manavgat Özel Bilgi Hastanesi, Antalya, Turkey

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*Corresponding author: Onur Özgenç, Dokuz Eylül University Hospital, Mesleki Beceriler, Inciralti, Mithatpasa Cad No 1606, 35340, Balçova, Izmir, Turkey, Tel:+90-532-4153169; Fax:+90 232 4129798; E-mail:ozgenc.onur@gmail.com

Abstract

In this case report authors wanted to draw attention, to extraintestinal disorders of Crohn's disease; an old disease known for more than a century, and to an emerging infectious pathogen *Nocardia*; a recently emphasized challenging species. A case of Crohn's disease with complicated skin disorders, and acute compartment syndrome and cervical epidural abscess evolving due to *Nocardia* bacterium, has been discussed.

The two medical entities, the Crohn's disease with its extraintestinal involvements and nocardial infection with potential risk to cause disseminated infection especially in the immune compromised host, are the main subjects of this manuscript.

In this respect, it is concluded that the patients with Crohn's disease should be monitored closely for their extraintestinal involvements, and emerging and fastidious infections, so that the role of those infectious pathogens in the etiology of Crohn's disease can be further investigated.

Keywords: Crohn's disease; Pyoderma gangrenosum, *Nocardia* infection; Acute compartment syndrome, Epidural abscess

Introduction

Inflammatory bowel diseases fall into the class of autoimmune diseases, in which the body's own immune system attacks elements of the digestive system. Crohn's disease is one of the principal type of inflammatory bowel disease that may affect any part of the gastrointestinal tract. Signs and symptoms often include abdominal pain, diarrhea, fever, and weight loss. Crohn's disease may also involve the skin, joints, eyes, blood, liver, kidney, and endocrine system. The skin rashes may be due to infections as well as due to Pyoderma Gangrenosum (PG) or erythema nodosum. Although the etiological factors causing these symptoms of Crohn's disease are not well known, it is suggested that genetic predisposition may play a role, or bacteria or viruses may trigger the disease symptoms [1,2,3].

Nocardia is an environmental bacterium found in water, decaying plants, and soil. In an immune compromised host this

bacterium, being an opportunistic pathogen, can cause severe and progressive nocardial infections [4,5]. This aerobic filamentous bacterium is gram-positive and acid-fast with modified Kinyoun stain [4,6]. When aerial hyphae forming colonies on solid medias are detected not shorter than few days of incubation, the clinical microbiologist should judge on clinical and laboratory basis whether the bacteria are colonizing or infecting agents [7]. Therefore, in the absence of suspicion, the identification of *Nocardia* bacteria could be missed by the clinician, because the diagnoses of nocardial infections with conventional techniques have limitations [8].

Case Report

First admission

A 58-years old female referred to infectious disease clinic of a teaching and research hospital with high fever, abdominal pain, bloody diarrhea, and ulcerated lesion on the left forearm (12X5cm). The next day, wound developed depth and forearm swelled with severe pain and paresthesia. A diagnosis of Acute Compartment Syndrome (ACS) was made by the physical examination of a consulting orthopedic surgeon. With a rapid decision, she was taken into the operating room, and fasciotomy and deep surgical debridement of the lesion on her forearm were performed. After few days, her clinical status became more stable and she was undergone colon-sigmoidoscopy. The histopathological report confirmed Crohn's disease with superposing signs of pseudomembranous colitis (Table 1). Neither she nor her relatives gave suspicious medical history of inflammatory bowel disease.

On admission the Erythrocyte Sedimentation Rate (ESR) was 58 mm/h. Blood results showed leukocytosis (14600 mm³), predominantly neutrophils, elevated C reactive protein (45 mg/dL), and anemia. Except moderate hypoproteinemia and minimum elevation of creatinine phosphokinase, all biochemical tests were within normal ranges. The direct stained specimens obtained for bacteriological culture revealed Gram-positive beaded small rods

and coccoid fragments within leukocytes. Ziehl–Neelsen stained preparations were negative. The bacterium from pus material grew on blood agar as small chalky white colonies with musty odor, and also grew on Loewenstein–Jensen medium and on corn meal agar as a pure culture within one week. The filamentous branching rods were seen with Ziehl–Neelsen with 1% sulphuric acid (modified Kinyoun technique) stained preparations, a typical feature of nocardiae (Table 2). The cultures were kept incubated for 3 more weeks. With the formation of aerial hyphae the bacterium was identified as *Nocardia* spp. [4,9]. The strain was reported as sensitive to cefotaxime, ceftriaxone, cefepime, imipenem, meropenem, vancomycin, teicoplanin, erythromycin, clarithromycin, rifampicin, minocycline, doxycycline, linezolid,

and resistant to trimethoprim/sulphamethoxazole (TMP/SXT), amikacin, tobramycin, ciprofloxacin, and levofloxacin with standard disk-diffusion susceptibility testing.

The patient was on treatment with ampicillin-sulbactam. Then following bowel biopsy report and information obtained from clinical microbiology laboratory the treatment was switched to ceftriaxone and vancomycin combination. The response to this regimen was good. The colitis resolved and the wound started healing. Within one month of systemic and topical wound therapy, the open wound on forearm was nearly closed. Upon discharge from the hospital, the maintenance therapy with doxycycline and teicoplanin was prescribed for two more weeks. She was advised to come for follow-ups.

Second admission

After two years, the patient (who did not show up for control examinations) presented again with the complaints of abdominal pain and bloody diarrhea. She told that she went to local doctors and she was under antibiotics therapy for her diarrhea. She was followed for two days with mild gastrointestinal discomfort and on the third day she had high fever, and pain and inflammation on her right dorsal foot and ankle (13x6 cm). On examination she also had some limitations on her neck movements, and appearance of scar on her left forearm due to healing of her previous wound. With these findings soft tissue ultrasonography for right foot and cervical magnetic resonance imaging were planned. The inflammation on right dorsal foot showed worsening within one day, spontaneous pus drainage started. The gastroenterologist and dermatologist visiting the patient diagnosed the lesion as Pyoderma Gangrenosum (PG), complication of Crohn's disease. In addition to ceftriaxone regimen, prednisolone 1mg/kg was started. The orthopedic surgeon followed the wound for topical treatment and prognosis, and bone involvement was not observed on x-ray examination. On Magnetic Resonance Imaging (MRI) of the cervical vertebrae on C5-6 and T1-2 levels, epidural collection (51x11 mm) was reported. The antibiotics implemented were meropenem, vancomycin, and linezolid. The bacteriological blood and pus specimens from wound did not reveal any growth. The leukocytosis and high CRP detections at the beginning of the symptoms returned to normal levels after 4 weeks. The wound defined as PG improved totally within 45 days. There was no abscess formation on the repeated MRI of the cervical vertebral column after two months, and the physician reported complete regression of her cervical neck stiffness. The patient who was in well being was discharged from the hospital with doxycycline, clarithromycin, and teicoplanin maintenance therapy for two additional weeks, which the *Nocardia* bacterium isolated at the first hospital admission was susceptible to all antibiotics in the regimen. She was followed up regularly for six more months with no complaints.

Discussion

Crohn's disease may involve any part of the digestive system, and commonly affects the terminal ileum and colon [1,3,10]. The inflammation of the intestine usually appears before the age of 30. Only the small proportion of people may develop the

Table 1: Schematic summary of the clinical observations and the implemented therapy of the Crohn's disease and the nocardial infection.

Symptoms and Findings	Diagnosis	Primary therapy
First admission		
High fever		
Abdominal pain, Bloody diarrhea	Crohn's disease and pseudomembranous colitis	IV* fluid replacement therapy
Ulcerated lesion on the left forearm	ACS** and Nocardial infection (bacteriological culture positive)	Fasciotomy and debridement Ceftriaxone, vancomycin, doxycycline
Second admission		
High fever		
Abdominal pain, Bloody diarrhea	Crohn's disease	IV fluid replacement therapy
Pain and inflammation on the right dorsal foot and ankle	PG***	Ceftriaxone Prednisolone
Limitation on neck movements	Nocardial cervical epidural abscess (culture not available)	Meropenem, vancomycin, linezolid
*IV; Intravenous **ACS; Acute Compartment Syndrome ***PG; Pyoderma Gangrenosum		

Table 2: The identification process of *Nocardia* bacterium from the wound specimen of the left forearm.

Microscopy		Bacteriological culture	
Direct	Small rods and coccoid fragments within leukocytes	Within 1-week of incubation	Small chalky white colonies with musty odor
Gram staining	Gram-positive, beaded, filamentous branching rods		
Acid-fast staining: 1) Ziehl-Neelsen 2) Kinyoun	Negative Positive	Within 3-weeks of incubation	Aerial hyphae formation

disease between the ages of 50 through 70. Although the cause is unknown there are some evidences that the disease could be triggered by a microorganism on hereditary basis [1,3].

The 58-years old patient had severe onset of inflammatory bowel disease without medical history of frequent diarrhea in the past, and neither the relatives developed the disease. On first admission to the hospital the patient had pseudomembranous colitis with underlying Crohn's disease. She also had ACS evolving on nocardial soft tissue infection. It is known that there is predisposition to pseudomembranous colitis in patients with inflammatory bowel diseases [11]. At that point authors could discuss that the symptoms of pseudomembranous colitis were due to severe Crohn's disease or those symptoms were triggered by the bacterium [1,2]. If bacterium was the cause, since crohn is an inflammatory disease, could it be Nocardia? For the exact answer the investigators had to grow *Nocardia* bacteria in large quantities in the stool. Since no stool culture for that fastidious microorganism was taken into consideration; to attribute the cause of pseudomembranous colitis to *Nocardia* bacteria could only be commentary. Meanwhile, a fulminant nocardial colitis case, reported in a woman patient with past history of Crohn's disease [12], seemed to support the authors' hypothesis.

Acute compartment syndrome is a rare complication usually following trauma, circulation disorders, burns, or sometimes invasive infections [13], which requires immediate surgery [14]. It develops as a result of increased interstitial tissue pressure in a closed anatomic compartment, so surgical decompression is needed [15]. Although urgent fasciotomy is indicated, in the presence of infection it is controversial [16]. So, in addition to fasciotomy deep surgical debridement is necessary. Here in, the nocardial skin infection was complication of Crohn's disease which is an autoimmune disorder. In PubMed/MEDLINE search of nocardial infections in patients with Crohn's disease, although infrequent, there are few reported cases [17,18], and this is the only described case of ACS in relation to nocardial infection. In the present case the bacterium is isolated from the cutaneous infection with suspicion of the authors, who are clinical microbiologists with previous experience with *Nocardia* bacteria [19,20].

On patient's second admission to the hospital the remarking clinical finding was PG. Pyoderma gangrenosum is rapidly developing ulcerative, necrotic, and painful dermatosis with surrounding erythema. The etiology of this sterile, neutrophilic process is unknown [21]. Sometimes it mimics necrotizing fasciitis [22]. Very rarely PG and necrotizing fasciitis-like opportunistic fungal infections are observed within skin biopsy specimens of the same host [23]. Our patient's wound presumed to be sterile but the patient was under pressure of antibiotics. Meanwhile, a good therapeutic response was achieved with antibiotics regimen along with prednisolone.

The most serious finding of the patient was epidural abscess formation diagnosed early in the course with the onset. Although the etiological agent could not be isolated because of the high dose of antibiotic implementation, the medical history of the

case lead the authors to nocardial Central Nervous System (CNS) infection. Nocardiosis of the CNS, although is seen infrequently is a life-threatening disease in patients with weak immune systems; in those the fatality rate is more than 85% [5]. To best of our knowledge, there is only one reported Crohn's disease case with cerebral nocardiosis [24]. With early antibiotic combination the patient's epidural abscesses within the cervical location of the spinal column was treated successfully, otherwise, the patient might have needed neurosurgical emergency.

All infrequent disorders coincidentally met in one Crohn's disease case is discussed. The extraintestinal disorders of the disease in conjunction with *Nocardia* bacterium is evaluated. Although not fully documented, the relationship of *Mycobacterium avium* subspecies *paratuberculosis* (MAP) with Crohn's disease is underlined by many investigators [2,3,10,25]. It is debated that anti-MAP antibiotics can play role as a therapeutic agent in the course of the inflammatory colitis [3]. The MAP from *Mycobacteriaceae* and *Nocardia* species from *Nocardiaceae* families are both in aerobic actinomycetes group [9]. Further studies on molecular basis are needed to designate the role of these infectious pathogens in the etiology of Crohn's disease.

The authors conclude that the patients with Crohn's disease should be monitored closely for their extraintestinal involvements, and emerging and fastidious infections.

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