

Nocardia infections among immunomodulated inflammatory bowel disease patients: A review

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Abstract

Human nocardiosis, caused by *Nocardia* spp., an ubiquitous soil-borne bacteria, is a rare granulomatous disease close related to immune dysfunctions. Clinically can occur as an acute life-threatening disease, with lung, brain and skin being commonly affected. The infection was classically diagnosed in HIV infected persons, organ transplanted recipients and long term corticosteroid treated patients. Currently the widespread use of immunomodulators and immunosuppressors in the treatment of inflammatory diseases changed this scenario. Our purpose is to review all published cases of nocardiosis in immunomodulated patients due to inflammatory diseases and describe clinical and laboratory findings. We reviewed the literature concerning human cases of nocardiosis published between 1980 and 2014 in peer reviewed journals. Eleven cases of nocardiosis associated with anti-tumor necrosis factor (TNF) prescription (9 related with infliximab and 2 with adalimumab) were identified; 7 patients had inflammatory bowel disease (IBD), 4 had rheumatological conditions; nocardia infection presented as cutaneous involvement in 3 patients, lung disease in 4 patients, hepatic in one and disseminated disease in 3 patients. From the 10 cases described in IBD patients 7 were associated with anti-TNF and 3 with steroids and azathioprine. In conclusion, nocardiosis requires high levels of clinical suspicion and experience of laboratory staff, in order to establish a timely diagnosis and by doing so avoid worst outcomes. Treatment for long periods tailored by the susceptibility of the isolated species whenever possible is essential. The safety of restarting immunomodulators or anti-TNF after the disease or the value of prophylaxis with cotrimoxazole is still debated.

Key words: Nocardiosis; Immunomodulation; *Nocardia* spp.; Inflammatory diseases

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Core tip: Opportunistic infections in immunomodulated patients with inflammatory diseases has gained renewed interest because of the new biological therapies. Concerning inflammatory bowel disease, in particular anti-tumor necrosis factor drugs, turned granulomatous infection diseases a real risk. The awareness and knowledge about nocardiosis, a rare but severe granulomatous infection, is probably lacking for the majority of doctors treating these patients. Our aim is to increase the awareness about the infection and review the published cases in this particular group of patients. We would like that our reads increase knowledge about clinical manifestations and up-to-date treatment, be aware of the risk of the disease and when to suspect nocardiosis.

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INTRODUCTION

Human nocardiosis is generally recognized as an opportunistic disease close related to immune dysfunctions, however any host may be affected. The infection can range from a sub-clinical infection to acute life-threatening disease^[1].

Classically the infection was more common in patients living with human immunodeficiency virus (HIV) infection, organ transplant recipients and those on long-term corticosteroid therapy^[2]. Concurrent use of immunosuppressants, preexisting pulmonary diseases and diabetes mellitus are also associated with increased risk of nocardiosis^[3].

The incidence of *Nocardia* infection is low, nevertheless early diagnosis and treatment in immunosuppressed patients is essential, due to its high morbidity and mortality^[4]. *Nocardia* infection causes granulomatous diseases and differential diagnosis should be made with more frequent granulomatous diseases, like tuberculosis^[5] and Crohn's disease. After the introduction of anti-tumor necrosis factor drugs (TNF- α) an increase in the incidence of granulomatous infections, including nocardiosis^[5] was noticed.

Our purpose is to focus on the descriptions of nocardiosis in immunomodulated patients due to inflammatory diseases and to review published cases in this setting.

RESEARCH

We searched PubMed, B-On, OVID databases

for articles till November 2014, using these key words alone or in combination: "*Nocardia* spp.", "nocardiosis", "immunosuppressed patients", "nocardia diagnosis", "nocardia treatment", "nocardia sensibility", "inflammatory bowel disease", "Crohn Disease", "ulcerative colitis", "anti-TNF therapy". We selected review articles of nocardiosis and 14 articles of case reports all in English language except one case report, all together 50 articles.

NOCARDIA SPP: THE BACTERIA AND PATHOGENIC MECHANISMS

Nocardia species are ubiquitous soil-borne aerobic microorganisms which belong to a large group of bacteria, aerobic actinomycetes, with more than 80 different species of *Nocardia* identified, of which at least 33 species are pathogenic^[6]. The majority of *Nocardia* infections are caused by inhalation, but some may be acquired by percutaneous inoculation after direct contact with soil. *Nocardia* species can spread hematogenously from lung parenchyma, particularly within the upper lobes, or from cutaneous infection sites to the brain, kidneys, joints, bones, soft tissues and eyes causing disseminated nocardiosis^[7]. Bacteria dissemination has been related to immunocompromising conditions as cell-mediated response and macrophages function^[2]. Therefore, patients under corticosteroids, in which macrophage and T-cell function are decreased, and patients treated with infliximab, an inducer of apoptosis of macrophages and T cells, are at risk of developing nocardiosis^[8]. The need for continuous immunosuppressive therapy, disseminated disease and central nervous system involvement^[9] are factors associated with poor prognosis. In a review of 10 cases of nocardiosis occurring in rheumatic patients 6 out of 10 had disseminated disease when their pulmonary lesion was diagnosed^[10].

CLINICAL ASPECTS

Nocardiosis may have several clinical presentations^[7]. (1) pulmonary Nocardiosis: in more than two-thirds of cases the lungs are the primary site of nocardial infection; the onset of the disease may be subacute or chronic and it is not distinguished by any specific signs or symptoms. Fever, weight loss, anorexia, dyspnea, cough, and haemoptysis^[2] may be present. Radiographic findings of lung involvement may include single or multiple nodules, lung masses (with or without cavitation), reticulonodular infiltrates, interstitial infiltrates, lobar consolidation^[7] (Figure 1). Brain imaging should be performed in all patients with pulmonary nocardiosis as cerebral dissemination is frequent and the bacteria seems to have a special tropism for neural tissue^[9]; (2) cerebral Nocardiosis: CNS is involved in approximately 20 percent of

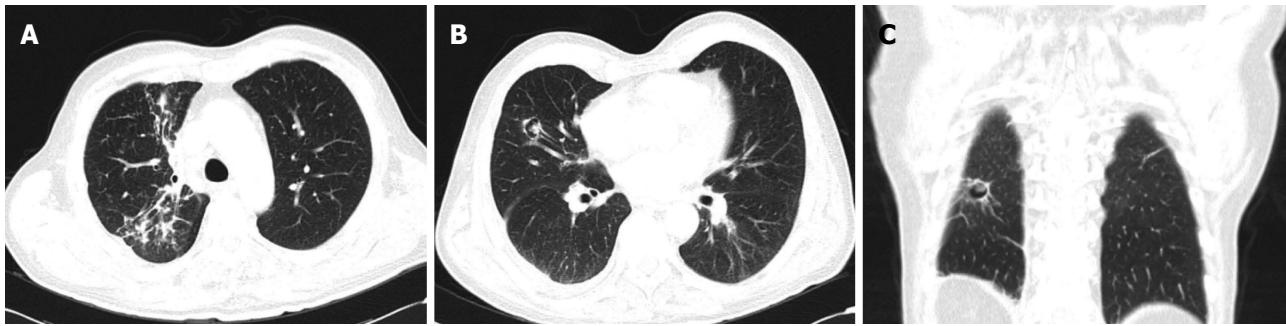


Figure 1 Torax computed tomography scan 73-year-old man with disseminated nocardiosis (cutaneous, pulmonary and cerebral involvements). A: Consolidations in upper right pulmonary lobe; B: Cavitation with heterogenous filling in right upper pulmonary lobe; C: Coronal image showing a cavitation in right lower pulmonary lobe.

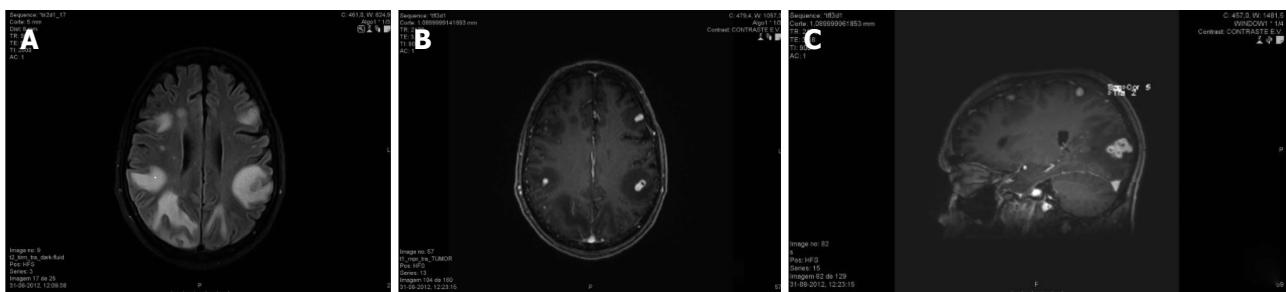


Figure 2 Cerebral magnetic resonance of 73-year-old man with disseminated nocardiosis (cutaneous, pulmonary and cerebral involvements). A: Axial T2 FLAIR (Fluid attenuated inversion recovery). Multiple focal lesions in bilateral fronto-parietal subcortical white matter, with prominent edema and mass effect resulting in sulcal effacement; B: Post-gadolinium T1 3D-MPRAGE, axial reformat. Ring enhancing lesions were depicted in post-contrast images; C: Post gadolinium T1 3D-MPRAGE, sagittal reformat. Ring enhancing lesions were depicted in post-contrast images, forming clusters in right occipital lobe.

nocardiosis and in 44 percent of disseminated cases^[9]. Most commonly it results from dissemination of infection from a pulmonary or cutaneous site. Cerebral lesions are parenchymal abscess that can occur in any region of the brain^[9] (Figure 2). Signs and symptoms of nocardial brain abscess are diverse and nonspecific: fever, headache, meningismus, seizures, and/or focal neurologic deficits. Nocardial meningitis is rare and can occur with or without an associated brain abscess^[11]. The clinical presentation is a subacute or chronic meningitis and the cerebrospinal fluid is similar to other bacterial meningitis^[11]; and (3) skin and cutaneous Nocardiosis: cutaneous disease most commonly results from direct inoculation of organisms into the skin after trauma in immunocompromised individuals. Primary infections usually present as superficial painless cellulitis or abscess with localized lymphadenopathy, and progress slowly^[7].

Disseminated nocardiosis is defined as two or more noncontiguous sites of involvement that may or may not include a pulmonary focus. There are no pathognomonic signs or symptoms of nocardiosis. The infection should be suspected in any patient who has brain, soft tissue, or cutaneous lesions, and a concurrent or recent pulmonary lesion. Pulmonary nocardiosis may mimic an exacerbation of an underlying lung disease, like chronic obstructive pulmonary disease^[12] and pulmonary sarcoidosis^[13]. Nocardiosis may be misdiagnosed as tuberculosis (since upper lobe involvement is common

and *Nocardia* spp. are weakly acid fast), invasive fungal disease and malignancy^[2].

NOCARDIA LABORATORIAL DIAGNOSIS

Nocardia spp. appear as delicate, filamentous, branching gram-positive rods in clinical specimens^[6]. The bacteria, like *Mycobacterium*, *Corynebacterium*, *Rhodococcus*, *Gordona* and *Tsukamurella*, members of the Nocardiidae actinomycetes subgroup, are all variably acid-fast on appropriate staining^[7]. However acid-fast staining property of *Nocardia* is often lost in older cultures^[1]. Growing of *Nocardia* species in culture is slow and incubation should be carried out for at least two weeks, and ideally cultures should be maintained for 4-6 wk before they are read as negative. Therefore, when *Nocardia* infection is suspected, the laboratory should be notified for specific culture media and staining procedures. For instance some sputum decontamination solutions are toxic to *Nocardia* spp., particularly sodium hydroxide, N-acetylcysteine and benzalkonium chloride^[2]. Curiously *Nocardia* spp. only rarely can be recovered in blood cultures despite frequent hematogenous dissemination^[14]. Most cases of bacteremia are associated with central venous catheters or other endovascular devices^[14]. *Nocardia* species identification is essential as not all species are pathogenic and different *Nocardia* species and strains often have markedly different

Table 1 Usual susceptibility patterns of common *Nocardia* species in human diseases

Nocardia species	Susceptibility	Resistance	Ref.
<i>N. asteroides sensu stricto</i>	TMP-SMX, TGC, Amikacin Imipenem (64%-98%)	TGC	Lerner et al ^[2] Sorrel et al ^[43]
<i>N. farcinica</i>	Amikacin TMP-SMX, Minocycline	Tobramycin	Wallace et al ^[21] Lerner et al ^[2] Uhde et al ^[44]
<i>N. nova</i>	TMP-SMX, TGC, Imipenem, Amikacin Clarithromycin (96%)	TMP-SMX and TGC (53%)	Uhde et al ^[44] Wallace et al ^[21] Larruskain et al ^[46]
<i>N. brasiliensis</i>	TMP-SMX, Amikacin TGC (88%-100%), Imipenem (20%-30%)	Ceftriaxone (81%)	Uhde et al ^[44] Sorrel et al ^[43]
<i>N. transvalensis</i>	TMP-SMX (88%), Imipenem (90%), TGC (50%)	Amikacin	Sorrel et al ^[43] McNeil et al ^[47]
<i>N. otitidiscaziarum</i>	Amikacin, Minocycline	TMP-SMX	Lerner et al ^[2]

TMP-SMX: Trimethoprim-sulfamethoxazol; TGC: Third generation cephalosporins.

susceptibility patterns^[15]. Identification of the species is difficult when using routine phenotypic tests but identification based on conventional phenotypic and enzymatic tests enables for the rapid identification of the most common^[16]. Alternatively, polymerase chain reaction (PCR) for identification of *Nocardia* spp. permits faster results than the conventional methods^[17]. Susceptibility patterns of *Nocardia* varies among different species; the most common patterns of sensibility and resistance are detailed on Table 1. Results of laboratorial antimicrobial susceptibility testing of *Nocardia* should be interpreted with caution because few studies correlated *in-vitro* data with clinical outcome. Nevertheless, it should be pointed that susceptibility of all *Nocardia* spp. to trimethoprim plus sulphamethoxazole, amikacin and linezolid has been confirmed by several studies^[6,15,18-20], whereas susceptibilities to beta-lactams, other aminoglycosides, ciprofloxacin and clarithromycin varied markedly^[15]. From 93 *Nocardia* isolates in clinical specimens, belonging to 15 strains of *Nocardia* spp., activity of beta-lactams was variable, with 89% of isolates being susceptible to imipenem, 84% to amoxicillin + clavulanate, 55% to ceftriaxone, 50% to amoxicillin and 9% to piperacillin + tazobactam^[15]. High-level of resistance to beta-lactams, including ceftriaxone and imipenem, was found in reference strains of *N. brasiliensis*, *N. otitidiscaziarum* and *N. niigatensis*^[15]. Also *N. farcinica* characteristically demonstrates resistance to third-generation cephalosporins and is often resistant to imipenem^[15,21,22]. Antimicrobial susceptibility testing is recommended as a guide to therapy for severe disease, refractory cases and for patients who are intolerant to treatment with trimetroprim-sulphamethoxazole^[15]. Susceptibility testing is particularly important in patients infected with *Nocardia* species that have high frequencies of antimicrobial resistance, such as *N. farcinica*. Drugs to be tested by microdilution are: amikacin, amoxicillin-clavulanate, ceftriaxone, ciprofloxacin, clarithromycin, imipenem, linezolid, minocycline (which predicts doxycycline susceptibility), sulfamethoxazole or

trimethoprim-sulfamethoxazole, and tobramycin^[23].

THERAPY

Trimethoprim-sulphamethoxazole (TMP-SMX) is the first line option and can therefore be used as an initial empirical treatment in patients with extensive disease, including brain abscess. It has been reported that this drug has excellent penetration into most tissue compartments, including the central nervous system, and high serum concentrations even after oral administration (recommended oral dose: 2.5-5 mg/kg of the trimethoprim component orally twice daily). Concerning endovenous TMP-SMX the doses should be similar to the treatment of pneumocystosis (15 mg/kg per day of the trimethoprim component in two to four divided doses). There have been few reports of patients failing to respond to TMP-SMX^[24]. Although, in patients with life-threatening disease and in those failing treatment, sulfonamide levels should be monitored. A sulfonamide level measured two hours after a dose should have a serum concentration between 100 and 150 mcg/mL^[2]. If the patient is allergic to sulfonamides, desensitization should be performed. For patients infected with sulfonamide-resistant *Nocardia* spp. or those who are allergic to sulfonamides, imipenem (500 mg IV every six hours) plus amikacin (7.5 mg/kg iv every 12 h) is an option.

Cutaneous infections

Oral TMP-SMX or amoxicillin-clavulanic acid are the drugs of choice for 1 to 3 mo in the case of mild cutaneous disease. Immunocompromised patients must be treated for a minimum of six months to one year.

Severe nocardia infections

Severe nocardiosis refers to some cases of pulmonary disease, all cases of disseminated disease or central nervous system disease, and infections involving more than one site in immunocompromised patients. In severely ill patients combined therapy with endovenous

Table 2 Clinical forms of Nocardiosis related to anti-TNF therapy in inflammatory bowel disease, rheumatic and psoriatic patients

Clinical form	Anti-TNF						Ref.
	IFX or ADA duration of therapy	Age	Associated treatment	Nocardia isolation	Outcome		
Cutaneous							
IBD-P	IFX -3 infusions	45	No	<i>Nocardia</i> spp.	Favourable	Singh et al ^[30]	
	IFX- 1,5 yr	61	No	<i>Nocardia</i> spp.	Favourable	Ali et al ^[31]	
R-P	IFX -3 yr	70	Metothrexate + steroids	<i>N. otitidiscauriarum</i>	Favourable	Fabre et al ^[32]	
Pulmonary							
IBD-P	IFX - 8 mo -6 infusions	77	Steroids	<i>N. asteroides</i>	Favourable	Stratakis et al ^[33]	
	IFX - 3 infusions	53	Azathioprine + steroids	<i>N.cyriacigeorgica</i>	Favourable	Parra et al ^[34]	
	IFX - 6 mo	81	6-mercaptopurine	<i>Nocardia</i> spp	Favourable	Saleemuddin et al ^[35]	
R-P	ADA - 4 mo	63	Steroids (DPOC)	<i>N. asteroides</i>	Favourable	Doraiswamy et al ^[48]	
Disseminated							
R-P	ADA ¹ - 4 mo	63	Metotrexate	<i>N. farcinica</i>	Favourable	Wendling et al ^[38]	
P-P	IFX ² - 2 mo	66	Alefacet 6 mo before	<i>N. farcinica</i>	death	Al-Tawfiq et al ^[37]	
IBD-P	IFX - 5 infusions	73	Prednisolone methotrexate	<i>N. asteroides</i>	Favourable with sequelae	Sidney et al ^[49]	
Hepatic							
IBD-P	IFX ≤ 1 mo	23	Steroids	<i>N. farcinica</i>	Favourable	Nakahara et al ^[36]	

¹Previously was treated with 3 mo of etanercept; ²Diabetic patient. IBD-P: IBD-patients; R-P: Rheumatologic patients; P-P: Psoriatic patients.

drugs with activity against *Nocardia*, like amikacin, imipenem, meropenem, ceftriaxone or cefotaxime is advisable^[7]. Initially treatment with two intravenous drugs is recommended by some authors^[2,6]. For more severe infection, even three intravenous drugs should be used^[6]. When the severe infection does not involve CNS initial treatment may consist of TMP-SMX (15 mg/kg iv of the trimethoprim per day in two to four divided doses) plus amikacin (7.5 mg/kg iv every 12 h). An alternative would be imipenem (500 mg IV every 6 h) plus amikacin^[2]. When there is CNS disease TMP-SMX plus imipenem is an option. Amikacin may be associated in case of multiorgan involvement.

SURGERY

In several settings surgical intervention may be needed: (1) cerebral or some large soft tissue abscesses that do not respond to antibiotic therapy^[25]; (2) empyemas and mediastinal infection with fluids; and (3) pulmonary nocardiosis complicated by pericarditis, which is almost always fatal if pericardial drainage is not performed^[26].

TREATMENT DURATION

The optimal duration of antimicrobial treatment for severe disease has not been clearly settled. Drugs should be switched to oral medication 3 to 6 wk after initial endovenous therapy and maintained for at least 6 to 12 mo in the case of cerebral or extensive disease. Immunocompromised patients may require longer courses of initial IV therapy (3 to 6 mo, depending on the extent of the disease, and clinical response) and the addition of amikacin, or a carbapenem or ceftriaxone may be advisable. All immunocompromised patients (except those with isolated cutaneous infection) and all patients with CNS

involvement should be treated for at least one year^[2].

RISK OF NOCARDIA RELAPSES

Because of the relapsing nature of *Nocardia* infection, long duration antimicrobial treatment is recommended. The need for continuation therapy in those who need re-introduction of immunosuppressors is not well settled. Some authors recommend prolonged oral maintenance therapy to prevent relapse of nocardiosis in patients who continue to be immunosuppressed as a result of their disease or treatment^[27]. TMP-SMX is the drug of choice but protection is not complete and it is not known the most appropriate regimen^[27]. Thus, in patients whose immunosuppression cannot be reversed, a maintenance regimen of TMP-SMX one single strength tablet daily if the *Nocardia* isolate is susceptible to TMP-SMX is the choice^[28]. Alternative maintenance regimens have not been systematically evaluated, although doxycycline 100 mg daily is a possible alternative.

NOCARDIOSIS IN PATIENTS UNDER ANTI-TNF- α

Nocardiosis is an infrequent complication in patients with chronic inflammatory diseases under anti- TNF- α agents. A total of eight cases of nocardiosis were identified among approximately 300000 patients treated with anti-TNF agents with a rate of 3.55 and 0.88 per 100000 treated patients with infliximab or etanercept, respectively^[5,29]. To our knowledge 10 cases were published (Table 2). Following infliximab therapy three cutaneous cases of nocardiosis were published: two in IBD patients^[30,31], and the other in a rheumatic patient^[32]. Three pulmonary nocardiosis cases^[33-35] and one hepatic nocardiosis^[36] have been reported in IBD patients under infliximab therapy. Disseminated nocardiosis was described following

Table 3 Clinical cases of nocardia disease in inflammatory bowel disease patients: Literature review

Ref.	IBD	Age (yr)	Sex	Medication	<i>N. species</i>	Clinical form	Treatment (duration)	Evolution
Vohra et al ^[40]	CD	16	F	6-Mercaptopurine 6 wk steroids	<i>N. asteroides</i>	Brain abscess; calf abscess	TMP-SMX + ceftriaxon: not established	Favourable
Stack et al ^[41]	UC	68	M	Cyclosporine, steroids	<i>N. asteroides</i>	Pulmonary (abcess)	Amikacin + cefotaxime-3 wk followed by cefuroxime 3 mo	Favourable
Singh et al ^[30]	CD	45	M	Infliximab 6 wk	<i>N. spp.</i> (polymerase chain reaction)	Cutaneous	TMP-SMX, 3 yr	Favourable
Stratakos et al ^[33]	CD (DM)	77	F	Infliximab 8 mo, steroids	<i>N. asteroides</i> (+ <i>Pneumocystis jiroveci</i>)	Pulmonary	TMP-SMX, 6 mo	Favourable
Parra et al ^[34]	CD	53	F	Infliximab, azathioprine, steroids	<i>N. cyriacigeorgica</i>	Pulmonary	TMP-SMX + amikacin + imipenem - 6 wk followed by TMP-SMX, 7.5 mo	Favourable
Arora et al ^[42]	UC	61	F	Azathioprine, steroids	<i>N. nova</i>	Cutaneous, abscess: brain lung, renal, pancreatic	TMP-SMX, 1 yr	Favourable, remission 2 yr after treatment
Nakahara et al ^[36]	CD	23	M	Infliximab, < 3 wk, steroids	<i>N. farcinia</i>	Liver nocardiosis	TMP-SMX for? not known	Favourable
Ali et al ^[31]	CD	61	M	Infliximab > 1 yr	<i>N. spp.</i>	Cutaneous	TMP-SMX for 6 mo	Favourable, restarted anti-TNF after therapy
Saleemuddin et al ^[35]	CD	81	M	Infliximab (3 mo) 6-mercaptopurine	<i>Nocardia</i> spp.	Pulmonary	TMP-SMX for? not known	Favourable; 5 mo after restarted anti-TNF under TMP-SMX; ok 1 yr after diagnosis
Sidney et al ^[49]	CD	73	F	Infliximab (5 infusions) Prednisolone methotrexate	<i>Nocardia asteroides</i>	Disseminated: Pulmonary cerebral	TMP-SMX for? not known	Favourable with sequelae

TMP-SMX: Trimethoprim-sulfamethoxazole; DM: Diabetes mellitus; CD: Crohn's disease; UC: Ulcerative colitis.

infliximab treatment in one case of psoriasis^[37] and in another of rheumatoid arthritis^[38]. One patient with disseminated nocardiosis did not survive: he was a man, 66-year-old, on infliximab due to psoriasis^[37]. Outside immunologic diseases it was reported a disseminated nocardiosis in a patient with alcoholic hepatitis treated with etanercept^[39].

NOCARDIOSIS IN PATIENTS WITH IBD

In patients with inflammatory bowel diseases to the best of our knowledge nine cases had been reported. Three cases were reported in patients under immunomodulation (steroids in two associated with 6-mercaptopurine/azathioprine and in one with cyclosporine^[40-42]) and two of them were disseminated. Six other cases were associated with anti-TNF: two cutaneous forms were under anti-TNF alone^[30,31] and four with anti-TNF combined with immunomodulators (steroids, thiopurines), with pulmonary disease in three cases and hepatic disease in one^[33-36] (Table 3).

Seven out of nine patients had a diagnosis of Crohn colitis with median age of 49 (61 if not considering

the teenager) years-old and 5 were male. All but two patients, with cutaneous forms, were under two or more immunomodulatory drugs. Six patients were under steroids and six under anti-TNF. Pulmonary nocardiosis was the most common clinical form of Nocardiosis, described in 44% of patients. *N. asteroides* was isolated in 3 patients, *N. farcinica*, *N. cyriacigeorgica* and *N. nova* in one case each. Two patients restarted anti-TNF therapy: one under TMP-SMX, 5 mo after starting Nocardia therapy and the other after 6 mo of therapy with TMP-SMX.

CONCLUSION

Nocardiosis is an uncommon disease caused by a Gram positive bacteria with acid-fast staining properties and diagnosis requires high levels of suspicion and experience of laboratory staff. The clinical impact of the disease is partly unknown, suggesting an underestimating of the real role of nocardiosis in human diseases. Persons under immunomodulation or immunosuppressive therapy require, as those with HIV, organ transplant re-

cipients, patients with pulmonary diseases and diabetes mellitus, special attention concerning the risks of nocardiosis. Remarkably double or triple immunosuppression seems to represent a higher risk for the disease. When concerning patients treated with anti TNF alone, just two cases of cutaneous forms were described. The most common clinical presentations are pulmonary and cutaneous, but the bacteria has the ability to disseminate and affect any organ, in particular the central nervous system. Laboratorial diagnosis is based on the identification of the bacteria (that growths slowly) on biological products, rarely on blood, and in alternative by PCR. The optimal duration of antimicrobial treatment for severe disease is not established but a prolonged course (one year) is advisable, because of the relapsing nature. There are several unanswered questions in nocardiosis infection as the safety of restarting immunomodulators or anti-TNF or the value of prophylaxis with TMP-SMX claiming urgent attention from physicians and investigators devoted to infection and immunological diseases.

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