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Listeria Monocytogenes Disease in a Patient Treated with Adalimumab

Marco Distefano, MD*
Infectious Disease Department, ASP 8, Siracusa, Italy

***Corresponding author:** Marco Distefano, MD, Infectious Disease Department, ASP 8 Siracusa, via Testaferrata, 1, 96100 Siracusa, Italy, Tel: 00390931724213, E-mail: erdis@tin.it

Abstract

Background: *Listeria monocytogenes* is an uncommon Gram-positive pathogen that causes self-limited febrile gastroenteritis in healthy hosts. *Listeria* is also a cause of invasive disease, including bacteremia and central nervous system infection in individuals at the extremes of age (neonates and older adults), immunosuppressed patients, and pregnant women. The mortality of invasive disease caused by *Listeria monocytogenes* is 20-40%. TNFα blockers are a new class of immunosuppressant drugs considered the most significant therapeutic advance in the care of IBD and rheumatologic disorders. Few cases of invasive listeriosis are reported after adalimumab (a monoclonal antibody anti-TNFα) therapy.

Case presentation: A patient with ulcerative colitis developed pyrexia, headache, and neck stiffness a few days after his first adalimumab subcutaneous administration. The patient had eaten packaged saladgreens and raw anchovies three days before treatment, and *L. monocytogenes* meningitis was diagnosed based on positive CSF cultures. Intravenous amoxicillin clavulanate improved the symptoms, and the patient was discharged without neurological sequelae.

Conclusion: Listeriosis associated with adalimumab is a potentially fatal condition. *Listeria* should be considered when a patient is taking immunosuppressive therapy and develops gastroenteritis, sepsis, or meningitic symptoms. As usually reported, symptoms started rapidly after adalimumab, suggesting that the patient already carried the bacteria before anti-TNFa therapy. The summary of product characteristics should include a recommendation to patients to avoid foods associated with *Listeria* at least one month after treatment but also the last weeks before treatment.

Keywords: Meningitis, Treatment, Adalimumab, Adverse events, *Listeria monocytogenes*

Abbreviations

CIOMS: Council for International Organizations of Medical Sciences**;** SPC: Summary of Product Characteristics**;** WHO: World Health Organization

The Gram-positive bacteria *Listeria monocytogenes* cause listeriosis usually contracted from unpasteurized dairy products, or products contaminated with *L. monocytogenes* after pasteurization, like soft cheeses or raw fish and meat. People with defective cellular immunity may develop septicemia, meningitis, or encephalitis, with a mortality rate ranging from 20 to 40% [1,2]. Immunocompetent persons rarely develop severe symptoms. Unless recognized and treated promptly, many patients who develop *Listeria* meningitis are left with significant neurological sequelae.

The importance of listeriosis associated with TNFα inhibitors has recently been reported to VigiBase©, the World Health Organization international database of adverse drug reactions (adverse events reported in 2.4% of patients) [3]. Listeriosis must be suspected in patients who develop pyrexia during treatment with adalimumab, even in the absence of meningism. A Summary of Product Characteristics (SPC) revision should be done to inform about the risk of this potentially fatal complication.

Case Presentation

A 49-years-old man was diagnosed with ulcerative colitis in 2012. He was treated with steroids without good results. Treatment was changed to adalimumab, a fully human monoclonal antibody inhibiting the action of TNFα, one week before his presentation to the emergency room. There was no other significant personal history. Some days after the injection of adalimumab, he became sick with sudden onset of abdominal pain, nausea, and fever up to 40 °C. At admission to the hospital, he was awake and hadphotophobia, neck stiffness, and other meningeal irritation signs were positive (Brudzinsky,

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Kernig). He was febrile (39.5 °C) and clinically dehydrated but normotensive. Physical examination revealed the absence of skin rash; flaccid paralysis was not present. His blood tests at admission revealed markedly elevated levels of C-reactive protein (CRP) and procalcitonin and are resumed in Table 1. As he did have neurological symptoms, brain imaging and lumbar puncture were performed. The cerebrospinal fluid (CFS) sample contained 1364 leucocytes/µl (lymphocytes + monocytes) and 100 red blood cells/µl, 42 mg/dl of protein, and 32 mg/dl of glucose (blood glucose, 98 mg/dl). The fluid pressure was 140 mmH_2O. Gram staining of the cerebrospinal fluid revealed the Gram-positive rods (Figure 1). Empirical treatment was started with acyclovir, ceftriaxone (2 gr q12hr), vancomycin (15 mg/kg q12 hr), and amoxicillin-clavulanic acid (2 gr q4hr). Empiric dexamethasone (10 mg QID) was also administered for the first four days of therapy. The level of consciousness improved. A CT scan ruled out space-occupying lesions. Magnetic resonance imaging (MRI) of the brain was done after four days of therapy, not detecting hyperintensity or areas of restricted diffusion in the cerebral cortex or periventricular or deep white matter (Figure 2). Antibodies (anti-Jo-1, anti-Sm, anti-SS-A, anti-SS-B, anti-nRNP, anti-Scl-70, anti-c-ANCA, anti-pANCA, anti-dsDNA, anti-amphiphysin, anti-CV2, antiPNMA2, anti-Yo (PCCA-1), anti-Hu (ANNA-1), anti-RI (ANNA-2), and anti-ganglioside) were negative. Electromyography (EMG) performed on the fifth evolution day was normal. Cerebrospinal fluid (CFS), serum, and whole-blood samples were analyzed for the identification of possible etiologies. Gram staining of CSF shows the presence of Gram rod, which was identified as *L. Monocytogenes*. After starting treatment, symptoms disappeared. Cefalea lasted one week, and the performance status rapidly improved. Vancomycin, ceftriaxone, dexamethasone were stopped soon, but amoxicillin-clavulanate was continued for 20 days and stopped after his general condition had remained stable for several days. The patient was subsequently discharged without any neurological sequelae.

Table 1: Biochemical values out of range at patient admission.

Biochemistry	Value	Normal value
WBC	21.2 10^3/mcl	4-11
Neutrophils	84%	42-76
Creatinine	1.8 mg/dL	0.7-1.2
Glucose	98	70-110
procalcitonine	25.32 ng/ml	< 0.1
K	2.8 mmoL/L	3.5-5.5
LDH	472 UI/L	0-247
CRP	442 mg/L	0-5
INR	1.54	0.8-1.2
AST/ALT	114/55 UI/L	0-50

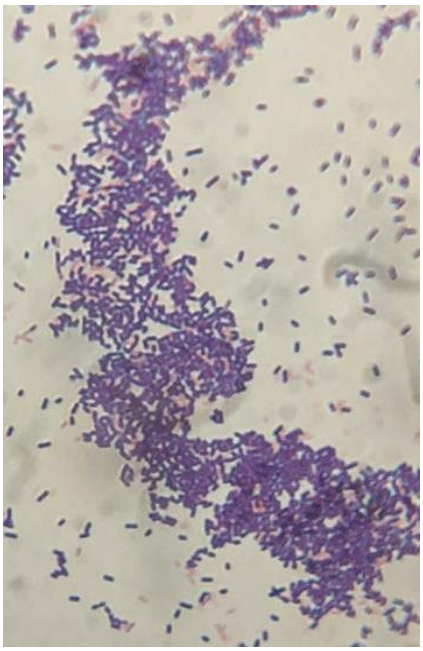

Figure 1: Gram staining of CSF revealed Gram positive Rods.

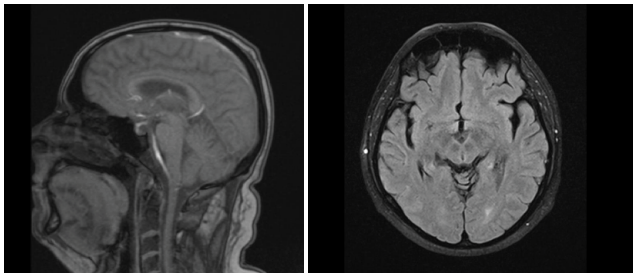

Figure 2: Magnetic resonance imaging (MRI) of the brain was negative.

Four months later, the patient had a complete recovery. The results of the microbiological assessment were as follows. Firstline investigation: gram stain and bacterial culture, alpha-herpesvirus (herpes simplex virus 1, herpes simplex virus 2, and varicella-zoster virus), and enterovirus were negative. Treponema pallidum and Cryptococcal neoformans (serum and CFS), Mycoplasma pneumoniae, Epstein–Barr virus, and Cytomegalovirus were negative. Screening for HIV (serology and RNA), hepatitis A, B, and C, and Mycobacterium tuberculosis (CSF) was also negative.

Discussion

Adalimumab is a human monoclonal antibody of the class of TNFα antagonists, a class of biologic agents that include infliximab, etanercept, certolizumab, and golimumab. TNFα blockers inhibit the inflammatory cascade by inactivation of TNFα. They are used to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and juvenile idiopathic arthritis. Since TNFα blockers are immunosuppressants, patients treated

are at increased risk of serious infections, including fatal. Bacterial, mycobacterial, fungal, viral, and other opportunistic pathogens can cause serious illness when a person's immune system has weakened. Various organ systems and sites can be involved. All these infections are considered contraindications to starting TNF inhibitors. In 2010 the British Society of Rheumatology published data from his registry that showed that cumulative incidence of tuberculosis was higher in patients treated with adalimumab than those treated with infliximab, etanercept of DMARD. Adalimumab is probably the most potent TNF blocker, determining the most significant breakdown of granuloma and the release of virulent organisms determining the highest risk of TB reactivation [4]. Recently, FDA reviewed cases of infection due to *Listeria monocytogenes* in patients treated with TNFα blockers. A search of the English-language database identified 26 published cases of *Listeria* infection in TNFα blocker-treated patients, including meningitis, bacteremia, endophthalmitis, and sepsis [5-10]. Seven fatalities were reported in patients receiving concomitant immunosuppressive drugs. Furthermore, FDA identified fatal *Listeria* infections in a review of data regarding pre-marketing phase 2, phase 3 clinical trials and post-marketing surveillance. In September 2011 the U.S. Food and Drug Administration (FDA) updated the *Boxed Warning* for the entire class of TNFα blockers. *Legionella* and *Listeria* were included for all of the TNFα blockers and consistent information about the risk of severe infections were added.

We herein report a case of *Listeria* colitis in a patient receiving adalimumab that progresses to septicemia and meningitis. To our knowledge, this was the 2nd case of Listeriosis associated with adalimumab reported [3], and the 16th occurred in patients treated with TNFα inhibitors. This case suggested a critical clinical issue. *Listeria monocytogenes* can exacerbate the inflammation in patients with ulcerative colitis, invade the bloodstream, and cause septicemia and meningitis in patients with an immunosuppressed status. The prevalence of patients with ulcerative colitis has increased in recent years, and TNFα blockers are increasingly used to cure this patient. Adalimumab impairs the action of TNFα secreted by inflammatory monocyte and activated macrophage. We must alert for *Listeria* infections in patients taking these drugs, especially adalimumab.

In these patients, we performed a lumbar puncture and initiated active antibiotic therapy on the day of the onset of meningitis symptoms. He recovered without any permanent central nervous system damage. We suggest that the rapid onset of therapy might prevent neurological sequelae. Patients should avoid ingestion of uncooked or undercooked meats, soft cheeses, and unpasteurized dairy products the last weeks before therapy and for at least one month after treatment [11,12]. The incubation period of *L. monocytogenes* varies (1 to 70 days) [1]. Corticosteroids can prolong the persistence of *L. monocytogenes* after food exposure, routinely administered to patients with ulcerative colitis [13]. Our patient had eaten soft cheese and raw fish, both known sources of *L. monocytogenes*, three days before the first infusion and six days before the debut of the symptoms. He did not consume any suspicious foods during the treatment cycle, and therefore most likely contracted the infection before the treatment. Patients should avoid eating such food items, not only after treatment. Outbreaks of *listeria* infections have been described to several food products, including deli meats, hot dogs, soft cheeses (including pasteurized cheeses contaminated after production), celery, sprouts and ice cream [14]. Exposure to *L. monocytogenes* might, therefore, be difficult to avoid [15].

Conclusion

L. monocytogenes can exacerbate inflammation in ulcerative colitis, invade the bloodstream and cause septicemia and infection in patients treated with TNFα inhibitors. Physicians and patients should consider the potentially lethal side effects of adalimumab. The SPC should be revised and advised patients to avoid foods associated with *Listeria* during and before treatment with adalimumab. The occurrence of listeriosis associated with adalimumab should be followed closely, and antibiotic prophylaxis could be considered if prophylactic measures are insufficient. An accurate diagnosis and the appropriate treatment of *Listeria* meningitis may preserve the function of the central nervous system (Table 2).

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Table 2: Food associated with listeriosis.

Common causes (large outbreaks)	Less common causes
Processed/delicaressen meats	Milk
Hot dogs	Ice cream
Soft Cheeses	Raw meat or fish
Patès	Sones fruites (eg, nectarines)
Canteloupe	Smoked sea food
	Corn and rice salad
	Packaged salad greens

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