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Amyotrophic Lateral Sclerosis: A Causal or Casual Relationship with Anti-Tnf Therapy?-A Clinical Case

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Abstract

Reports of coincident amyotrophic lateral sclerosis, rheumatoid arthritis, and anti-TNF treatment are scant. We report a new case of a patient with other comorbidities exposed to long-term adalimumab treatment in whom a potential neurotoxic side effect of the drug must be considered. We speculate whether continued exposure after the diagnosis of ALS could explain the severity of her outcome.

Keywords: Amyothrophic lateral sclerosis; Anti-TNF therapy; Adalimumab rheumatoid arthritis

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A 62-year-old woman with hypothyroidism, dyslipemia, and a depressive syndrome first consulted our rheumatology unit in July 2002. She had a 6-month history of seropositive rheumatoid arthritis treated with corticosteroids and NSAIDs. Physical examination revealed 7 NSJ, 12 NTJ, and ESR was 107 mm/h. Methotrexate therapy was started (to 15 mg s.c./w, maximum-tolerated dose) and hydroxychloroquine (400 mg/d) was added later with good response (1 NSJ, 2 NTJ, and ESR, 8 mm/ h). Methotrexate was replaced with cyclosporine A (100 mg/d) in January 2006 because of fatty liver (elevated gamma-glutamyl transpeptidase and compatible ultrasound scan), which was then replaced with azathioprine (50 mg/d) in August 2007 due to increased creatinine levels. In September 2007, after liver enzyme had normalized and a new polyarthritis outbreak (ESR, 79 mm/h) methotrexate treatment was reestablished in combination with adalimumab (40 mg, s.c./eow). In September 2008, she underwent a total left hip replacement. Two attempts to optimize anti-TNF therapy failed because of flares. In February 2010, methotrexate was replaced with hydroxychloroquine (400 mg/d). In April 2010, a basal cell carcinoma of the left eyelid and nose was excised. Being fully informed of the ACR 2008 guidelines [1], she decided to continue anti-TNF therapy with close monitoring and remained in remission.

In April 2012, after three years on adalimumab and sustained remission, the patient complained of progressively worsening muscle weakness; despite walking with a cane, she had frequent falls. In February 2015 she had difficulties swallowing that impaired her ability to eat and drink, accompanied by weight loss (17 kg in 6 months), dysarthria, and slurred speech. She had no urinary or fecal incontinence. Physical examination revealed global atrophy in the muscles of the arms, legs, and hand, and weakness; cachexia; hypomotility and fasciculations of the tongue; and hyperreflexia of the arms and normoreflexia of the legs. The cranial nerves were not affected, and there was no cognitive impairment.

Gastroscopy showed erosive antral gastritis and a feeding tube was placed by percutaneous endoscopic gastrostomy. Video fluoroscopic swallowing exam showed severe dysphagia with high risk of bronchial aspiration. Bulbar ALS was confirmed by signs of impaired swallowing: pharyngeal transit time and opening of the proximal esophagus were very delayed, and there was no upward or lateral motility of the tongue. There was bronchial aspiration during swallowing of 10 cc of pudding-consistency and pyriform sinuses contained 5 ml of food debris.

Electromyography showed an active lesion of the second motor neuron, affecting cervical, lumbar, and bulbar areas with severe axonal loss to the arms and legs. Magnetic resonance imaging showed signs of chronic hypoperfusion hypoxia with mainly subcortical grade 2 leukoaraiosis. The diagnosis of definite amyotrophic lateral sclerosis (ALS) was established in June 2015 by a neurologist, and adalimumab was discontinued. Infectious diseases and other muscular and neurological disorders were ruled out, and riluzole treatment was started. The patient died several weeks after the diagnosis.

Comments

Several cases of ALS have been reported in association with anti-TNF treatment for inflammatory rheumatic diseases. Dziadzio et al. [2] reported a patient with rheumatoid arthritis who was diagnosed with ALS after receiving infliximab (initially 3 mg/kg, 8-weekly, later increased to 5 mg/Kg) for 5 years. Loustau et al. [3] reported a case in a patient treated with TNFalpha blockers for ankylosing spondylitis. And Padovan et al. [4] reported another

case in a patient with rheumatoid arthritis treated with infliximab (initially 3 mg/kg, 8-weekly, increased to 5 mg/kg after 8 months), developing after 12 months after the start of treatment and 4 months after the dose was increased.

In 2012 the European system for reporting suspected adverse drug reactions, the Eudra Vigilance database, received several reports of ALS in relation to treatment with TNF-alpha inhibitors, mainly for rheumatoid arthritis [5]. The exact number of cases is uncertain due to possible duplicate reporting (adalimumab 13–18, etanercept 25–31, infliximab 20–24 cases, and others), although, on the other hand, adverse drug reactions often go unreported. In 2014 Arkema et al. [6] found no association between rheumatoid arthritis, ALS, and anti-TNF treatment in Swedish National Registries; however, their data had very wide confidence intervals and they concluded that it remains unknown whether treatment with anti-TNF modifies the presentation or clinical course of ALS after its onset. Furthermore, they determined cases of ALS by searching the national patient register or cause-of-death register for the International Classification of Diseases(ICD) codes for ALS; they admitted that some cases of ALS might had been misclassified although they carried out a sensitivity analysis. Our patient's clinical, electromyographic, and imaging studies met the "El Escorial" criteria for definite ALS (one upper motor neuron sign and lower motor neuron signs in three regions, progressivity, and exclusion of other disease processes) [7]. Our patient was exposed to adalimumab for 3 years after her first symptoms of ALS developed (8 years in total), and we do not know whether this could explain the severity of her outcome. The cause of ALS is unknown, although a potential neurotoxic side effect of anti-TNF must be considered, given the potential protective role of TNF in the CNS [8]. Thus, the question is, apart from stressing prompt diagnosis, whether or not to continue anti-TNF after ALS has been diagnosed?.

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