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CASE STUDY

Multiple Sclerosis-Like Neurologic Symptoms In a Rheumatoid Arthritis Patient On Etanercept

Ripudaman Munjal, MD;[1] Chad Walker, DO;[2] Gagan Dhillon, MD;[1] Shraddha Rayamajhi, MD;[1] Wasique Mirza, MD;[1] Sunil Kumar, MD;[3] Madhukar Reddy Kasarla, MD;[4] Kiran Panuganti, MD;[5] Abhijeet Ramanujam, MD;[6] Gaurav Jain, MD;[7] Sumit Fogla, MD;[8] Shashank Kraleti, MD;[9] Naveen Patil, MD;[10] Sudheer Reddy Koyagura, MD, MPH;[11] Arun Chaudhury, MD[12]

[1]Department of Internal Medicine, The Wright Center for Graduate Medical Education, Scranton, Penn.; [2]Regional Hospital of Scranton, Scranton, Penn.; [3]Neshoba County Hospital, Philadelphia, Miss.; [4]Parkway Surgical and Cardiovascular Hospital, Wise Health System, Fort Worth, Tex.; [5]Presbyterian Hospital (Texas Health), Denton, Tex.; [6]Woodland Memorial Hospital, Sacramento, Cal.; [7]Berkshire Medical Center, Pittsfield, Mass.; [8]Beaumont Hospital, Grosse Pointe, Mich.; [9]UAMS, Little Rock, Ark.; [10]Arkansas Department of Health, Little Rock, Ark.; [11]Northwest Arkansas Medical Center, Bentonville, Ark.; [12]GIM Foundation, Little Rock, Ark.

Keywords Altered mental status, diplopia, drug adverse effect, biologics, TNF alpha antagonist

Abstract

We report the case of a 35-year-old gentleman who developed fatigue, cognitive changes described as "fogginess," unilateral headache, same-sided facial numbness and diplopia on left lateral gaze, while on the tumor necrosis factor alpha (TNF-α) antagonist etanercept for management of long-standing rheumatoid arthritis. MRI of brain, MR angiography of cerebral circulation, and analyses of cerebrospinal fluid (CSF) were normal. No oligoclonal bands were detected in the CSF. C reactive protein and sedimentation rates were normal. Lyme titer was positive and 43 and 66 kDa IgG antibodies were detected. The decision was taken to stop etanercept. In addition, the patient was treated with ceftriaxone for presumed Lyme disease. Though no frank evidence of demyelination was obtained, the symptom complex resembled presentation of multiple sclerosis. Tumor necrosis factor (TNF)–α inhibitors belong to a class of disease-modifying antirheumatic drugs that have revolutionized the treatment of inflammatory rheumatologic disorders. Despite their clinical benefit in rheumatologic conditions, TNF-α inhibitors have been implicated in the development of CNS and peripheral nervous system disorders. Clinical alertness shall help to detect and avoid cataclysmic neurologic adverse outcomes related to anti-TNF–α therapy.

Introduction

Biologics, targeting and antagonizing a specific biologic pathway, are a common class of medications in current medical care. These medications are considered relatively safe and have well-defined side effect(s). However, unpredictable adverse effect(s) (A/Es) may arise, thus necessitating alertness and clinical suspicion during their clinical use. Here we describe such an associative condition in which an adult male patient with long-standing rheumatoid arthritis on chronic disease control with the TNF–α (tumor necrosis factor alpha) antagonist etanercept developed sub-acute altered mental status, fatigue and unilateral headaches, facial pain, and diplopia on lateral gaze.

Case report

A 35-year-old, well-built male individual with a pleasant personality, and history of polyarticular joint disease due to seronegative rheumatoid arthritis for the last 16 years was admitted to our hospital for evaluation of persistent headache and visual symptoms. The patient initially presented with left unilateral daily headache around the left eye radiating to the back of the left occiput described as a squeezing, pressure sensation; left-sided facial pain and numbness, and left-sided diplopia for four-to-six-week duration. His primary care physician started him on Fioricet and nortriptyline, which did not improve the symptoms. The headache seemed to be worse in the night. He denied any chest pain, nausea, vomiting, or cough. He was initially provided with a provisional diagnosis of migraine and treated accordingly. However, there was no improvement of symptoms. There was associated cognitive impairment and emotional lability, described by the subject as low energy, decreased concentration, and "fogginess," which prompted for hospital admission for evaluation of altered mental status.

The patient had a long-standing history of inflammatory polyarthritis. He was on chronic steroid therapy and a presentation consistent with sero-negative symmetric inflammatory polyarthritis. Alongside, the patient had co-existing proximal muscle weakness and elevated CPK, thus inflammatory myopathy being in the differential. Earlier, in August 2013, prednisone was stopped. The patient was bridged with Medrol, which was gradually tapered and then started on Enbrel (etanercept) for management of joint disease. The patient had no known drug allergies (only documented allergy was to cashew), no rashes or psoriasis.

The patient was on etanercept for approximately the last 28 months. During his hospital admission for evaluation of these emergent conditions including diplopia, detailed eye examination was performed. His fundus examination was normal. Cranial nerves examination revealed full extraocular movements, but diplopia on left gaze. Using a red glass test, it localized the abnormal image to abduction of the left eye, likely involving dysfunction of the sixth cranial nerve. Facial sensation reported a decrease in pinprick over V1 and V2 on the left side. Motor examination revealed full power in the upper and lower extremities with intact reflexes. The neurologic symptoms were presumed to be related to the use of etanercept and a decision was taken to stop the

biologic agent. The symptoms improved, and he did not have any headache, but he still complained of diplopia and fatigue two months after the hospital course. Neurological examination including cranial nerve examination was normal two months following discharge. Behavioral evaluation at this time revealed normal mood and affect, language, thought and cognition.

During the hospital stay, notable labs included: (i) an elevated total bilirubin (1.08 U/L) and liver enzymes (AST 51 U/L, ALT 169 U/L); (ii) a low HDL cholesterol (13.5 mg/dl); other lipid parameters within normal limits (LDLc 83.7 mg/dl, cholesterol 114 mg/dl, triglyceride 77, cholesterol/HDL ratio 5.6); (iii) C reactive protein (CRP) was non-elevated at 0.29 mg/L; (iv) WBC count was 12.1 k/UL on day of admission (Neutrophils 87% and lymphocyte 6%); (v) D-dimer was unelevated at 0.26 ug/ml; (vi) the sedimentation rate was 0 ml/hr; (vii) negative ANA titer; (viii) Notable parameters in comprehensive metabolic panel (CMP) revealed glucose 138 mg/dl, HbA1C 5%, Calcium 9.8 mg/dl, Magnesium 2.2 mg/dl, TSH 0.66 UlU/ml.

Clear CSF was obtained by lumbar puncture (LP) performed by aseptic procedures under anesthesia. Notable finding during CSF examination was slightly elevated protein (50) and glucose (81). No oligoclonal band was detected by isoelectric focusing (IEF). Oligoclonal bands are usually present in the CSF in greater than 85% patients with the demyelinating disease multiple sclerosis. It may also be detected in brain tumor, infarction, CNS lupus, inflammatory polyneuropathy, and sub-acute sclerosing panencephalitis. CSF cultures were normal.

HIV1 and 2 IgG antibodies were undetected. RPR was non-reactive. Lyme antibody was detected (1.84; >1.10 is considered as positive). Further Lyme-specific antibodies were evaluated by western blotting. 41 kDa and 66 kDa IgG bands were detected; all other bands for IgM and IgG were negative.

Myelin basic protein was less than 2 mg/L. CSF IgG was 2.3 mg/dl, albumin CSF 23.8 mg/dl, IgG serum 773 and albumin serum 3.5 g/l, leading to IgG index of 0.44 (normal 0.66).

Routine MRI of brain without contrast and with Magnevist did not reveal any acute intracranial abnormality or abnormal enhancement. A few tiny foci of increased T2 and FLAIR signals was seen scattered throughout the cerebral hemisphere, which is a nonspecific finding seen in chronic migraine headaches. However, these findings may also be indicative of demyelination. There was no restricted diffusion to suggest infarction, no extra-axial collection, and normal vascular flow voids of the skull base. 3D time-of-flight magnetic resonance angiography (MRA) of the intracranial arterial vessels showed normal patterns of the vascularity of the circle of Willis, with a normal variation of the right posteroinferior cerebellar artery (PICA). Vertebral and basilar arteries showed normal dimension bilaterally without aneurysm.

The remainder of the hospital course involved insertion of a PICC for administration of ceftriaxone for suspected Lyme disease, though this consideration was low on the differential. USG abdomen revealed distended gall bladder with several gall stones. Blood culture during the hospital course had shown no growth.

The gentleman in discussion is a fitness instructor, lives at home with his wife, and has a pet dog. He denied any history of drug or tobacco use. Though numerous joint involvement due to rheumatoid arthritis, our patient is a lifestyle coach and actively participates in gym activities and golf. Important past medical history includes herpes zoster involving the face about five years ago. The patient did not remember the sidedness, although his wife reported that it might have been on the right side.

Discussion

The current report presents an associative condition of use of the biologic agent anti-TNF antagonist etanercept and development of diplopia and other neurologic symptoms resembling the heterogeneous presentation of multiple sclerosis. These could have resulted from the effects of etanercept. The only correlative evidence we can offer in support of this association is that the patient's symptoms considerably improved after cessation of the medication.

The role of cytokines in maintenance of myelination is being increasingly appreciated. Thus, cytokine antagonists may cause demyelination, involving both cranial and peripheral nerves.[1,2] We ruled out preliminary demyelinating disorders like multiple sclerosis by negative oligoclonal bands as well as normal CSF IgG index. The third, fourth and sixth cranial nerves traversing through the cavernous sinus derives its blood supply from adjacent vessels.[3] MR angiography revealed intact basilar vasculature, as well as the internal carotids and normal cavernous sinuses. The lipid parameters for our patient was also normal. The likelihood that an acute or acute-on-chronic vascular disorder resulting from metabolic dysfunction affecting the nerve supply of the cranial nerves supplying the extraocular muscles, leading to the visual disturbances, was likely low. Two months after the episode, clinical evaluation demonstrated normal function of cranial nerves, though the left pupillary reaction to light was somewhat sluggish.

Whether etanercept contributed to cognitive deficits cannot be predicted by the information obtained from our patient. The patient had no evidence of any cognitive deficit two months after the initial episode. The significance of the periventricular T2/FLAIR signals also remains unknown.

Earlier, a single report has identified extraocular myopathy leading to painful diplopia after the use of etanercept. Our report delineates a similar associative condition, though we remain unsure of whether demyelinating nerve disease involving the cranial nerves supplying the extra-ocular muscles or a myopathy per se was the cause of the development of the visual disturbances. The patient had other neurologic features, including headache and transient cognitive decline, without any frank neurovascular abnormality detected by imaging and routine neurologic evaluation. It is prudent to be aware about such situations, which may help in continued clinical care. MRI did not reveal any frank demyelination.

Though precision medicine has ushered in newer agents for pharmacotherapy catering to novel treatments for a wide variety of diseases, use of these agents should always be with caution. The present case highlights this issue. Complete information from package insert and other literature should be obtained prior to using these medications. Anti-TNF alpha based medications is now common pharmacologic drugs used for many autoimmune and inflammatory conditions, including arthritides of diverse etiologies. Anti TNF–α drugs have been associated with multiple sclerosis, optic neuritis, acute transverse myelitis, progressive multifocal leucoencephalopathy, and acute and chronic inflammatory demyelinating polyneuropathy.[1-2, 4-11] Precise neuroimmune interactions are not known. Despite high TNF–α levels in multiple sclerosis plaques and the cerebrospinal fluid, anti-TNF–α drugs seem to trigger MS and worsen its course.[10-12]

The development of neurological disorders in patients on anti-TNFalpha medications is stochastic in nature.[13-15] A recent study has shown that a certain type of single nucleotide polymorphism (SNP) on the TNF receptor increases susceptibility to demyelinating disorders, the mutated receptor itself acting in aberrant signaling leading to de-

velopment of multiple sclerosis-like symptoms. This SNP, (rs1800693) however, does not occur in rheumatoid arthritis or other autoimmune diseases like psoriasis or Crohn's disease.[14] This SNP, however, predisposes to primary biliary cirrhosis.[16] It has been proposed that this SNP may predispose to increased demyelination upon exposure to TNF antagonists.[14] Routine genotyping for these predisposing SNPs may not be clinically feasible.

Our patient continues to have multiple joint problems, including shoulder and hip pain, and frequent knee joint problems. Our patient was started on abatacept as an alternative biologic, after discussion of the possibility of use of tocilizumab, tofacitinib, and rituximab. The continued need for use of these biologics also raised suspicion for paraneoplastic condition, which is currently being evaluated.

In summary, the present case highlights that use of TNF–α agent etanercept may cause multiple sclerosis-like symptoms including fatigue and personality changes, sensory deficits, and neuromyopathy, including diplopia due to involvement of the cranial nerves supplying the extraocular muscles. Aggressive identification of evolving symptoms shall prevent adverse neurologic outcomes.

Addendum: The association and clinical presentation shall be reported to the FDA Medwatch.

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