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Clinical Short Communication

TNF-alpha inhibitor associated myelopathies: A neurological complication in patients with rheumatologic disorders

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ABSTRACT

Objectives: Tumor necrosis factor-alpha inhibitors (TNFα-I) are biological agents used in the treatment of rheumatologic disorders. TNFα-I have been associated with demyelinating disorders mimicking multiple sclerosis. The goal of this report is to illustrate cases of myelopathy which developed during the use of TNFα-I.
Methods: We describe the clinical, neuroimaging and laboratory features of 4 cases of myelopathy associated with TNFα-I.
Results: The mean period of TNFα-I exposure was 27 [12–36] months. Three of the four patients exhibited active inflammatory myelopathy as the spinal cord MRI lesions enhanced with gadolinium and CSF pleocytosis or oligoclonal bands were present. All patients had normal brain MRIs at the time of presentation.
Conclusions: TNFα-I may play a role in the development of myelopathies in absence of brain involvement or other features of demyelinating disease. TNFα-I associated myelopathy should be considered in patients with history of treatment with TNFα-I who exhibit symptoms of myelopathy.

1. Introduction

Tumor necrosis factor alpha (TNFα) is a cytokine that plays a key role in inflammatory response in various autoimmune diseases including rheumatoid arthritis (RA), psoriasis and Crohn's disease [1]. TNFα-I have been shown to be effective in patients with these conditions and their use has surged in the past few years [1,2]. Interestingly, there has been also an increase in reports of adverse effects with the use of TNFα-I which include a broad spectrum of neurologic syndromes including demyelinating disease mimicking multiple sclerosis [2,3]. Most of the reported cases of demyelinating disease had brain involvement and rarely presented with isolated inflammatory myelopathy or transverse myelitis [3,4]. We present 4 cases of isolated myelopathies which developed after the use of TNFα-I.

2. Methods

We performed a retrospective chart review of 458 patients seen from 2010 to 2015 at the Johns Hopkins Transverse Myelitis Center for the presumptive diagnosis of transverse myelitis. We identified 4 patients who developed new onset myelopathy associated with the use of TNFα-I. Patient imaging, laboratory data and clinical evaluation were reviewed.

For the purpose of this study, myelopathy was defined as a neurological syndrome consistent with dysfunction of the spinal cord. Myelitis, or inflammatory myelopathy, was defined as a myelopathy with objective evidence of an inflammatory component including cerebrospinal fluid pleocytosis, enhancement of lesions after gadolinium on MRI or the presence of oligoclonal bands.

This study was approved by the Johns Hopkins Institutional Review Board. All patients reported in this article gave their consent for publication.

3. Results

Pertinent clinical, demographic, neuroimaging and CSF characteristics, as well as TNFα-I drug use and treatment are summarized in Table 1.

3.1. Case 1 – acute multifocal myelopathy

A 52 year-old, Caucasian woman with a 10-year history of RA previously managed with NSAIDs, methotrexate and hydroxychloroquine was started on adalimumab due to poor control of her symptoms. Three years after initiation of treatment, she experienced acute onset of dysesthesias in both lower extremities and in the left side of the

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Table 1
Key characteristics of 4 new cases of myelopathy associated with TNFα-I.

Case	1	2	3	4
Age (years)/sex	52/F	52/F	42/M	54/F
Rheumatologic diagnosis	RA	Crohn's disease	RA	Lupus and RA
TNFα-I used	Adalimumab	Adalimumab	Adalimumab	Certolizumab
Exposure time	3 years	1 years	3 years	2 years
Neurological syndrome	Acute myelopathy-paraplegia.	Chronic myelitis - motor and sensory disturbance.	Chronic myelitis with sensory disturbance.	Chronic myelitis with sensory disturbance
Spine MRI T2W lesion distribution	Multifocal/C2-T1/dorsal columns.	Long ext./C7-conus/anterior cord.	Monofocal/C5/postero-lateral cord.	Monofocal/T7/lateral cord.
Spine MRI Gad +	No	Yes	Yes	No
Initial brain MRI	Normal	Normal	Normal	Normal
Follow up brain MRI	Normal	Normal	Normal	Normal
CSF WBC	1	117	11	0
CSF protein	Normal	72 mg/dl	Normal	Normal
CSF OCBs	Negative	Positive	Positive	Positive
CSF IgG index	Normal	0.7	0.59	1
Treatment/response	IVMp 250 mg qd × 6 days/partial	IVMp 1 g qd × 5 days/partial	Oral Mp/none. IvMp 1 g qd × 5 days/none	IVMp 1 g qd × 4 days/partial

RA: rheumatoid arthritis. MRI: magnetic resonance imaging. T2W: T2-weighted image. CSF: cerebrospinal fluid. WBC: white blood cells. IVMp: intravenous methylprednisolone. nl: normal. OCBs: oligoclonal bands. Long exten: longitudinal extensive. Gad +: lesion enhancement after gadolinium administration. Neg: negative.

chest. These sensory symptoms were followed by weakness and numbness from the waist down over a period of 12 h. Her initial physical exam was remarkable for a T8 sensory level, spastic paraplegia, brisk patellar and Achilles reflexes and urinary retention. Initial spinal magnetic resonance imaging (MRI) was negative. Three days later, a second spinal MRI showed multifocal hyperintense lesions on T2W sequences which involved mostly the posterior columns from C2 to T1 (Fig. 1). The lesions did not enhance after gadolinium administration. Initial brain MRI was normal. Cerebrospinal fluid (CSF) showed 1 white blood cell (WBC) per μL, protein at 37 mg/mL, IgG index <0.7 and absence of oligoclonal bands (OCBs). Treatment with intravenous methylprednisolone 1000 mg daily for 6 days was given with partial improvement in motor function. An extensive diagnostic workup revealed an elevated anti-cardiolipin IgM although other biomarkers were negative or normal including rheumatoid factor (RF), vitamins B12, B1, and B6, copper, folate and TSH. A second brain MRI one week later remained normal. Adalimumab was discontinued as it was considered a possible etiological factor. She opted for stopping all disease modifying therapies for her RA and continued with analgesic management only. Follow-up one year after presentation her motor function had mostly recovered, although she was left with residual bladder and proprioception dysfunction.

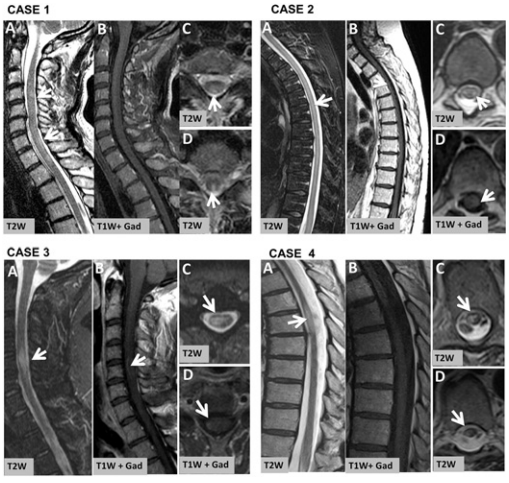

Fig. 1. Spinal cord MRI of the cases reported Case 1. Multifocal T2W signal intensity abnormalities in visualized in the dorsal columns of the spinal cord (A, C, D). No evidence of gadolinium enhancement was noted (B) Case 2. MRI showing longitudinally extensive T2W signal intensity abnormalities in the anterior and lateral spinal cord regions (A, C) with evidence of enhancement (B, D) Case 3. MRI showing a focal T2W hyperintensity in the right posterolateral spinal cord at C5 (A, C) which enhanced after gadolinium administration (B, D) Case 4. MRI showing T2W signal intensity abnormality in the right lateral aspect of the cord at T7 (A, C, D) without enhancement (B).

3.2. Case 2 - progressive longitudinal extensive myelitis

A 52 year-old Caucasian woman with a past medical history of type 2-diabetes mellitus (DM) and 25 years of Crohn's disease, had been initially treated with sulfasalazine and oral steroids. Adalimumab was introduced as treatment later due to recurrent flare ups despite initial treatment. One year later, she experienced generalized weakness and gait instability that evolved over 3 weeks to ataxia. Initial physical exam was remarkable for decreased pain and temperature sensation in an L4 dermatomal distribution, gait ataxia and urinary retention. Initial spinal MRI showed a T2W hyperintensity from T12–L1 with leptomeningeal enhancement. Brain MRI was normal. CSF showed 117 WBC per μL (95% lymphocytes), protein at 72 mg/dL, positive OCBs and IgG index <0.7. Intravenous methylprednisolone 1000 mg was given for 5 days with partial improvement. She then worsened over the next 6 months and developed marked paraparesis, at which point spinal MRI was repeated and revealed a longitudinally extensive lesion from C7 to the conus affecting mainly the anterior compartment of the spinal cord with some gadolinium enhancement (Fig. 1). Brain MRI was still normal. Repeat CSF showed persistent pleocytosis. She underwent diagnostic workup, including an extensive panel of autoimmune and rheumatological markers, including NMO antibody, which were negative. A chest CT scan was normal. Adalimumab was considered to be the cause of the myelopathy and was discontinued. Low dose oral prednisone was started for control of her rheumatological disease. Continued follow up over two years demonstrated improvement of her paraparesis and spasticity although there is still residual gait dysfunction. She did not fulfill criteria for multiple sclerosis on subsequent brain MRIs. The spinal cord lesions in MRI also improved although increased signal intensity abnormalities in both corticospinal tracts were noticed.

3.3. Case 3 – progressive focal myelitis

A 42 year-old Caucasian man with a past medical history of RA for 10 years, previously treated with oral prednisone and methotrexate, was transitioned to adalimumab due to persistent diffuse arthralgias despite medication. After 3 years on this treatment, he started to have progressive numbness and paresthesias in his right hand. Over the next weeks, his sensory symptoms spread to his forearm. He later developed intense pain and a Lhermitte sign. Initial physical exam was notable for mild weakness of the finger flexors and extensors muscle groups in the