RHEUMATOLOGY

Letters to the Editor

Rheumatology 2017;56:1428–1430
doi:10.1093/rheumatology/kex144
Advance Access publication 6 April 2017

Methotrexate-induced dysautonomia in a patient with rheumatoid arthritis

Rheumatology key message

- Methotrexate might worsen subclinical dysautonomia in patients with rheumatoid arthritis.

SIR, MTX is the first-line disease-modifying drug for most patients with RA. Although MTX only penetrates the blood–brain barrier poorly due to its hydrophilic properties, CNS side effects have been reported, especially for higher parenteral dosages. Also, this agent is known to yield neurotoxicity following intrathecal administration [1].

In January 2016 a 71-year-old man was admitted to our Syncope Unit because of repeated episodes of loss of consciousness, which had started 4 years before, subsequently worsening in intensity and frequency. His medical history included RA (diagnosed 5 years before), chronic obstructive pulmonary disease, hypertension and benign prostatic hyperplasia; his drug therapy included ramipril 5 mg daily, MTX 5 mg/week (started 5 years before) and alfuzosin 0.4 mg daily.

All the episodes of loss of consciousness were similar, with a very short or absent prodromal period; recovery was rapid, even though with partial retrograde amnesia. One episode was also characterized by loss of bladder control. There were no apparent precipitant events or triggers, except for a temporal relationship with the administration of MTX, as all the episodes occurred ~12 h following drug assumption.

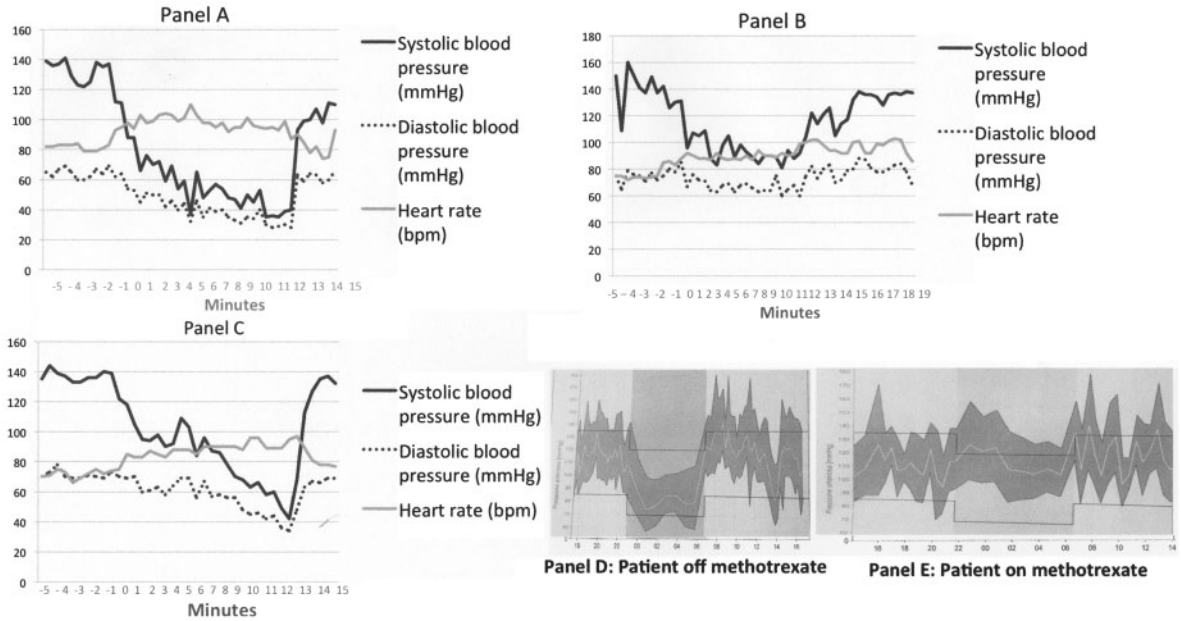
The patient had already undergone transthoracic echocardiography, electroencephalography, carotid US and brain MRI, with normal findings. All renal and liver function indices, as well as blood cell count and electrolytes, were normal. Twenty-four-hour Holter ECG monitoring, with measurement of heart rate variability, evidenced a significant reduction in both sympathetic and parasympathetic modulation. Thus, head-up tilt testing with video electroencephalograph (EEG) recording was performed. The patient developed a neurally mediated syncope after 14 min of passive orthostatism, with severe hypotension (systolic blood pressure = 40 mmHg) and no EEG abnormalities (Fig. 1 A). Therefore, alfuzosin was interrupted; as the patient stressed a time relationship with the administration of MTX, this agent was also withdrawn. After 2 months of well-being without any further syncopal episode, the patient repeated head-up tilt testing, which documented only asymptomatic orthostatic hypotension (Fig. 1B). Also, 24-h blood pressure monitoring showed a physiological circadian pattern with nocturnal fall (so-called dipping, Fig. 1D). Due to the relapse of arthritis, MTX was reintroduced, while the withdrawal of alfuzosin was confirmed. After 3 months without syncope, but with marked symptoms of fatigue and light-headedness, the patient underwent a new head-up tilt testing, during which he developed a vasovagal syncope after 13 min of passive standing, but with higher pressure values than in the first exam (Fig. 1C); in addition, 24-h blood pressure monitoring showed an abnormal, non-dipping pattern (Fig. 1E). According to these evidences, MTX was stopped and treatment with LEF was started. After 6 months, the patient was doing well; he reported no syncopal events nor fatigue, and a satisfactory control of his rheumatologic disease.

Neurological side effects during treatment with oral MTX are considered rare, yet dysautonomic symptoms may be more common, and underreported, in elderly patients [2]. In fact, subjective symptoms of toxicity have been reported by 20% of 25 patients receiving low-dose MTX therapy for inflammatory arthritis, while most neurotoxic effects may be subclinical [2]. The most common neuropathologic abnormality associated with MTX is disseminated or multifocal necrotizing leucoencephalopathy [3]. Other less frequently reported pathologic findings include diffuse parenchymatous degeneration with gliosis and axonal dystrophy, diffuse and focal subpial grey matter necrosis, mineralizing microangiopathy, dystrophic calcification and multifocal axonal hydropic swelling [3].

The pathogenesis of MTX-induced autonomic dysfunction is unclear, but several mechanisms have been proposed, including toxicity due to demyelinating neuropathy or leucoencephalopathy [3, 4]. Also, few cases of posterior reversible encephalopathy syndrome, probably due to endothelial damage, have been reported during the administration of low-dose oral MTX [5]. In addition, this drug might induce oxidative stress, thus increasing apoptosis [6]. Also, a well-known consequence of oxidative stress is lipid peroxidation, and white matter has a high lipid content. Of note, white matter changes have been associated with dysregulation of the autonomic nervous system [7].

Despite the interruption of alfuzosin and MTX, autonomic dysfunction was still present in our patient, as evidenced by the presence of orthostatic hypotension. Probably, such a dysfunction enhanced the adverse effects of MTX. In fact, an imbalance of the autonomic nervous system, characterized by increased overall sympathetic tone, decreased vagal activity and decoupling of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system has been reported in 26% of patients with

Fig. 1 Results of tilt testing and ambulatory blood pressure monitoring during the various drug regimens



(**A**) Initial head-up tilt testing, while the patient was taking both alfuzosin and MTX; (**B**) second head-up tilt testing, after the withdrawal of alfuzosin and MTX; (**C**) third head-up tilt testing, after the reintroduction of MTX; (**D**) 24-h blood pressure monitoring, after the withdrawal of alfuzosin and MTX; (**E**) 24-h blood pressure monitoring, following the reintroduction of MTX.

RA [7]. As MTX is a first-line treatment for RA, this interaction probably occurs more frequently than is commonly perceived by physicians.

In conclusion, autonomic dysfunction should be researched in rheumatic patients on MTX. Where present, its identification is crucial for improving a patient's safety and quality of life. Also, because the efferent vagus nerve yields a direct anti-inflammatory influence, also known as the cholinergic anti-inflammatory pathway [8], restoring parasympathetic activity might contribute to modifying the course of the rheumatic disease.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Alice Laudisio[1], Domenico P.E. Margiotta[2], Giuseppe Zuccalà[3], Antonella Afeltra[2] and Raffaele Antonelli Incalzi[1]

[1]*Unit of Geriatrics,* [2]*Unit of Allergology, Immunology and Rheumatology, Department of Medicine, Campus Bio-Medico di Roma University and* [3]*Department of Geriatrics, Neurosciences, and Orthopaedics, Catholic University of Medicine, Rome, Italy*

Accepted 3 March 2017

Correspondence to: Alice Laudisio, Unit of Geriatrics, Department of Medicine, Campus Bio-Medico di Roma University, via Álvaro del Portillo 21, 00128 Rome, Italy.
E-mail: lavoralice@gmail.com

References

1 Kinzel O, Verma RK, Wiest R, Mattle HP. Toxic cerebellar syndrome due to methotrexate. Pract Neurol 2015;15:214–5.

2 Wernick R, Smith DL. Central nervous system toxicity associated with weekly low-dose methotrexate treatment. Arthritis Rheum 1989;32:770–5.

3 Renard D, Westhovens R, Vandenbussche E, Vandenberghe R. Reversible posterior leucoencephalopathy during oral treatment with methotrexate. J Neurol 2004;251:226–8.

4 Sternberg Z. Promoting sympathovagal balance in multiple sclerosis; pharmacological, non-pharmacological, and surgical strategies. Autoimmun Rev 2016;15:113–23.

5 Hart C, Kinney MO, McCarron MO. Posterior reversible encephalopathy syndrome and oral methotrexate. Clin Neurol Neurosurg 2012;114:725–7.

6 Taylor OA, Hockenberry MJ, McCarthy K *et al*. Evaluation of biomarkers of oxidative stress and apoptosis in patients with severe methotrexate neurotoxicity: a case series. J Pediatr Oncol Nurs 2015;32:320–5.

7 Barnden LR, Kwiatek R, Crouch B, Burnet R, Del Fante P. Autonomic correlations with MRI are abnormal in the

brainstem vasomotor centre in Chronic Fatigue Syndrome. Neuroimage Clin 2016;11:530–7.

8 Koopman FA, Stoof SP, Straub RH *et al*. Restoring the balance of the autonomic nervous system as an innovative approach to the treatment of rheumatoid arthritis. Mol Med 2011;17:937–48.

Rheumatology 2017;56:1430–1433
doi:10.1093/rheumatology/kex154
Advance Access publication 18 April 2017

Immunoglobulin G4-related disease associated with extensive granulomatous changes

Rheumatology key message

- Extensive granulomatous changes may rarely be encountered in otherwise typical IgG4-related disease.

SIR, IgG4-related disease (IgG4-RD) is a relatively newly described condition characterized classically by the triad of lymphoplasmacytic inflammation, storiform-type fibrosis and obliterative phlebitis, with prominence of IgG4-positive plasma cells and an IgG4/IgG ratio of $>40\%$ on immunohistochemistry [1]. The presence of granulomas generally excludes the diagnosis of IgG4-RD [2]. Herein, we describe a markedly rare case of IgG4-RD associated with extensive granulomatous changes.

A 61-year-old man was admitted to our hospital with enlargement of the submandibular glands. He had never had previous exposure to tuberculosis, Bacillus Calmette–Guérin vaccination and organic solvents. One year previously, non-contrast CT had shown dilatation of the aortic root to a diameter of 53 mm, but not right hydronephrosis. Five months before admission, he had noticed enlargement of the right submandibular gland. Physical examination demonstrated a palpably enlarged right submandibular gland. ^{18}F-Fluorodeoxyglucose (FDG)-PET/CT revealed increased uptake in the right submandibular gland, around the outside of the aortic root and in foci adjacent to the common iliac arteries (Fig. 1A–D; arrow). Contrast-enhanced CT demonstrated a mass lesion corresponding to the FDG uptake partly surrounding the aortic root (Fig. 1E–G; arrow). Contrast-enhanced CT and FDG-PET/CT showed no hilar lymphadenopathy. The uptake along the common iliac arteries corresponded to a mass causing right ureteral obstruction and hydronephrosis. Laboratory results included elevated serum IgG4 (198 mg/dl), IgG (1963 mg/dl) and IgE (392.1 IU/ml), and showed normal hepatic function tests and negative tests for anti-SS-A/Ro, SS-B/La antibodies and ANCA. Submandibular gland biopsy demonstrated an extensive inflammatory infiltrate, rich in plasma cells with occasional lymphoid follicles (Fig. 1H and I). Obliterative phlebitis was also observed (Fig. 1J). Immunostaining revealed more than 100 IgG4-bearing plasma cells per high-power field (Fig. 1K) and $>40\%$ of IgG4/IgG-positive cell ratio (Fig. 1L and M). Extensive non-necrotizing granulomatous changes with CD68-positive Langhans-type giant cells were also noted against the background of storiform fibrosis (Fig. 1N and O). Ziehl–Neelsen staining for *Mycobacterium tuberculosis* and Grocott staining for fungus were negative. There was no evidence of lymphoma or vasculitis. Moreover, *M. tuberculosis* culture and PCR from submandibular gland tissue were negative. We diagnosed IgG4-RD with extensive granulomatous changes. The patient was treated with oral prednisolone 0.6 mg/kg, which dramatically reduced the prominence of the IgG4-RD lesions on CT and also lowered the serum IgG4 and IgG.

Our case illustrated clinically, serologically and histopathologically typical IgG4-RD except for many multinucleated giant cells (MGCs) and granulomas. A good response to CS contradicted the possibility of a granulomatous infectious disease, such as tuberculosis or ANCA-associated vasculitis, including granulomatosis with polyangiitis. In addition, the association of sarcoidosis was also very unlikely because of the unusual organ distribution that included the periaorta and retroperitoneum. Granulomas and MGCs are exceptional in IgG4-RD, and their presence would previously have made this diagnosis very unlikely [2]. However, some cases with typical IgG4-RD accompanied by MGCs have been recently reported [3, 4]. Some of these had a history of tuberculosis or RA, indicating that immune reactions to tuberculosis or rheumatoid nodules might be related to the disease initiation. It is thought that IL-4 and IFN-γ are crucial for MGC formation [5, 6]. The involvement of IL-4 is well known in the pathophysiology of IgG4-RD [7]. Furthermore, it was recently reported that lesional CD4$^+$ cytotoxic T lymphocytes secreted IFN-γ in IgG4-related dacryoadenitis and sialoadenitis [8]. Therefore, IL-4 and additional Th1 stimulation, which induces IFN-γ, might generate MGCs in patients with IgG4-RD.

In conclusion, extensive granulomatous changes may rarely be encountered in otherwise typical IgG4-RD. Close clinicopathological correlations are required to exclude the possibility of true granulomatous diseases mimicking IgG4-RD (e.g. sarcoidosis, granulomatosis with polyangitis) or coincidental development of the two conditions.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Yoshinori Taniguchi[1], Mitsuhiro Kawano[2], Yoh Zen[3], Natsuki Aoyama[1], Fumie Suehiro[4] and Yoshio Terada[1]

[1]*Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Nankoku,* [2]*Department of Rheumatology, Kanazawa University, Kanazawa,* [3]*Department of Diagnostic Pathology, Kobe University, Kobe and* [4]*Department of Internal Medicine, Kochi Kenshin Clinic, Kochi, Japan*

Revised version accepted 10 March 2017

Correspondence to: Yoshinori Taniguchi, Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Nankoku, 783-8505 Japan.
E-mail: taniguchiy@kochi-u.ac.jp