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Cytokine profiles of amyopathic dermatomyositis with interstitial lung diseases treated with mycophenolate

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Keywords
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Abstract

A 59-year-old Japanese man diagnosed with interstitial lung disease associated with amyopathic dermatomyositis with anti-melanoma differentiation-associated gene 5 (MDA-5) antibodies was treated with intravenous methyl prednisolone (PSL) 1000 mg, oral PSL 1 mg/kg, and oral cyclosporin 200 mg daily. His respiratory condition worsened after treatment with two times of intravenous cyclophosphamide and another steroid pulse therapy as well as PSL and cyclosporin. Addition of mycophenolate mofetil (MMF), 1.5 g daily improved PaO_2/FiO_2 (PF) ratio of the patient from 294 to 360 at 4 weeks and 416 at 15 weeks after addition of MMF. We measured cytokine concentration in preserved serum taken at 11 and 7 weeks before addition of MMF and at 4, 11, and 15 weeks after MMF administration. Of the 28 cytokines evaluated, the concentrations of fibroblast growth factors-2 (FGF-2), chemokine (C-X3-C motif) ligand 1 (CX3CL1), interleukin (IL)-1ra, IL-17A, inducible protein 10 (IP-10), and monocyte chemotactic protein-1 (MCP-1) decreased after addition of MMF. These results suggest that MMF may be beneficial to patients with interstitial lung disease by modification of the cytokine/growth factor protein expression.

Introduction

Patients with amyopathic dermatomyositis (ADM) with anti-melanoma differentiation-associated gene 5 (MDA-5) antibodies sometimes develop rapidly progressive interstitial lung disease (ILD) resistant to intensive therapy. Rapidly progressive ILD in ADM with anti-MDA-5 antibodies has been reported predominantly in Asia, especially in Japan [1]. Mycophenolate mofetil (MMF) improved pulmonary physiology in a large cohort of connective tissue disease-associated ILD (CTD-ILD) [2]. As MMF is approved only to those with organ transplants or lupus nephritis in Japan by means of health insurance policies, it is unclear whether MMF is also beneficial to the Japanese patients with ADM-ILD and anti-MDA-5 antibodies.

Case Report

A Japanese patient with ADM-ILD and anti-MDA-5 antibodies was successfully treated by addition of MMF to the treatment with corticosteroids, cyclosporin, and intravenous cyclophosphamide as previously summarized [3]. In brief, a 59-year-old Japanese man was diagnosed with and hospitalized for ADM-ILD with anti-MDA-5 antibodies. We administered him intravenous methyl prednisolone (PSL) 1000 mg for three consecutive days followed by 1 mg/kg oral PSL, and 200 mg oral cyclosporin. His respiratory condition worsened with a decrease of PaO_2/FiO_2 (PF) ratio and gradual emergence of subpleural consolidation in lower lobes even after treatment with two times intravenous cyclophosphamide, 500 mg, and another steroid pulse therapy as well as oral PSL and cyclosporin. We then added MMF, 1.5 g daily with approval by the Committee of Ethics, Niigata University (9 September 2009, no. 926). His PF ratio improved considerably with fading of consolidation in high-resolution computed tomography (CT) of the chest (Fig. 1).

We measured cytokine/growth factor (GF) protein concentration in preserved serum during his treatment with

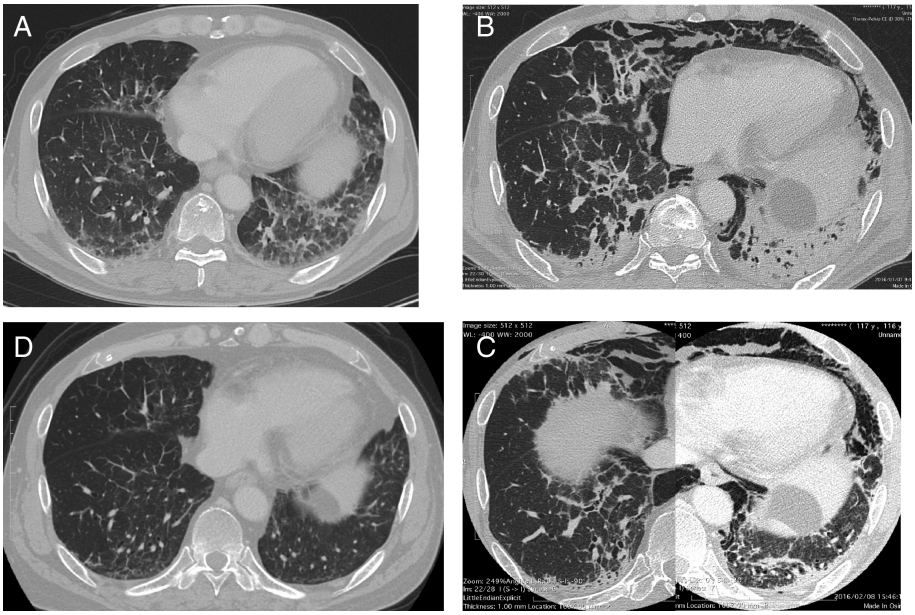

Figure 1. Chest computed tomography (CT) of a patient with interstitial lung disease associated with amyopathic dermatomyositis successfully treated by an addition of mycophenolate mofetil (MMF). Ground glass and linear opacities mainly in lower lobes deteriorated to subpleural consolidation even after treatment with high-dose prednisolone (PSL), cyclosporin, and intravenous cyclophosphamide with development of pneumomediastinum (A and B). However, they dramatically improved after MMF was added even during tapering of PSL (C and D). (A) One week after methyl PSL pulse followed by oral PSL, 60 mg daily and oral cyclosporine, 200 mg daily; (B) repeated steroid pulse therapy and intravenous cyclophosphamide, 500 mg two times with tapered PSL 40 mg and cyclosporine, 200 mg; (C) 3 weeks after addition of oral MMF, 1.5 g with oral PSL, 35 mg, and cyclosporine, 200 mg; and (D) 9 months later with MMF, 0.5 g, PSL, 15 mg, and cyclosporine, 100 mg. Panels (B) and (C) show composites of images of right and left lung at the same slice of chest CT.

the Milliplex Map Human Cytokine/Chemokine Kit (Merck Millipore, Darmstadt, Germany) according to previously described procedures [4]. Serum was taken and preserved frozen during his admission at 11 and 7 weeks before addition of MMF and at 4, 11, and 15 weeks after addition of MMF. The PF ratio of the patient decreased from 348 to 294 before addition of MMF, but improved to 360 at 4 weeks and to 416 at 15 weeks after addition of MMF. The assay is a novel multiplexed, particle-based, flow-cytometric assay named Luminex systems (Luminex Corporation, Austin, TX, USA), which utilizes anti-cytokine monoclonal antibodies linked to microspheres incorporating distinct proportions of two fluorescent dyes. The cytokines/GF proteins for which we measured concentration at each time point were as follows: epidermal GF, eotaxin, fibroblast growth factors-2 (FGF-2), FMS-like tyrosine kinase-3 ligand, chemokine (C-X3-C motif) ligand 1 - (CX3CL1), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-CSF (GM-CSF), growth-related oncogene, interferon-α2 (IFN-α2), IFN-γ, interleukin-1α (IL-1α), IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, IFN-γ inducible protein 10 (IP-10), monocyte chemotactic protein-1 (MCP-1), MCP-3, macrophage-derived chemokine, macrophage inflammatory protein-1α (MIP-1α), MIP-1β, sCD40L, sIL-2Rα, transforming GF-α, tumour necrosis factor-α (TNF-α), TNF-β, and vascular endothelial GF. Cytokines/GF proteins which had less than out of range (OOR) or more than OOR at more than one point were excluded. Of the 28 cytokines/GF proteins evaluated, the concentrations of FGF-2, CX3CL1, IL-1ra, IL-17A, IP-10, and MCP-1 decreased after addition of MMF. On the other hand, eotaxin and sCD40L increased after addition of MMF (Table 1).

Discussion

Japanese patients with ADM and anti-MDA-5 antibodies are likely to develop rapidly progressive ILD. Although MMF stabilizes and improves respiratory functions of CTD-ILD patients, it is not approved currently for Japanese patients with ADM-ILD. Gil et al. reported a case series of patients with ILD in ADM including a patient with anti-MDA-5 antibodies who received MMF as well as intravenous immunoglobulin [5]. Although the patient treated by Gil et al. died due to pneumonia 30 months after initial presentation, MMF could be a treatment option for patients with ADM-ILD and anti-MDA-5 antibodies.

Table 1. Changes of serum cytokine/growth factor protein concentrations during treatment.

	Week after addition of MMF					
Values	−11	−7	−1	4	11	15
PaO_2/FiO_2 ratio	348	320	294	360	416	NA
EGF	359.2	195.5	NA	197.3	316.8	287.8
Eotaxin	78.9	181.0	NA	241.4	254.8	249.9
FGF-2	83.1	95.4	NA	61.3	74.1	66.6
CX3CL1	83.4	254.1	NA	36.3	80.5	36.3
G-CSF	56.6	83.2	NA	32.7	77.7	46.2
GM-CSF	63.6	77.0	NA	28.0	67.3	31.3
GRO	2059.1	1685.8	NA	1154.8	1941.1	1340.0
IFN-α2	42.0	69.8	NA	21.1	80.2	32.3
IFN-γ	12.3	5.9	NA	8.9	8.9	5.2
IL-1β	<OOR	20.0	NA	1.1	82.5	12.2
IL-1ra	462.3	400.4	NA	75.4	169.3	48.2
IL-4	11.8	26.3	NA	0.2	28.7	6.0
IL-6	75.3	305.4	NA	7.3	190.4	42.3
IL-7	24.3	19.7	NA	12.0	24.0	17.7
IL-8	189.0	2465.2	NA	393.7	6366.3	2862.0
IL-9	0.43	1.38	NA	0.64	1.74	0.97
IL-10	56.9	7.6	NA	116.7	30.0	15.5
IL-12 (p70)	1.4	2.2	NA	3.4	5.8	0.8
IL-15	6.0	4.7	NA	8.4	7.0	4.7
IL-17A	73.3	104.7	NA	3.4	4.9	2.92
IP-10	5873.5	4626.1	NA	2236.5	2317.1	594.2
MCP-1	3342.4	3688.4	NA	2187.3	1325.9	939.1
MDC	675.8	130.6	NA	175.7	160.7	229.3
MIP-1α	67.5	448.2	NA	46.8	1875.7	714.8
MIP-1β	116.3	553.8	NA	98.7	1418.7	370.4
sCD40L	7644.5	4319.2	NA	9369.4	>OOR	9897.6
TGF-α	29.1	26.2	NA	20.8	32.7	25.4
VEGF	288.3	269.0	NA	175.0	315.7	265.0

Values are shown in pg/mL. Cytokine/growth factors which had <OOR or >OOR at more than one point were excluded. MMF, mycophenolate mofetil; EGF, epidermal growth factor; FGF, fibroblast growth factors; CX3CL1, chemokine (C-X3-C motif) ligand 1; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte macrophage-colony stimulating factor; GRO, growth-related oncogene; IFN, interferon; IL, interleukin; IP-10, IFN-γ inducible protein 10; MCP, monocyte chemotactic protein; MDC, macrophage-derived chemokine; MIP, macrophage inflammatory protein; TGF, transforming growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; NA, not applicable; OOR, out of range.

We treated a patient with ADM-ILD with anti-MDA-5 autoantibodies whose respiratory function and high-resolution CT findings dramatically improved after addition of oral MMF, 1.5 g daily [3]. The patient's respiratory condition deteriorated during treatment with PSL as well as other immunosuppressive agents, oral cyclosporin, and repeated intravenous cyclophosphamide. Cyclosporine, a calcineurin inhibitor, exerts its effects by interfering with T-lymphocyte function. Cyclophosphamide, an alkylating agent that prevents cell division by cross-linking DNA, produces immunosuppressive effects possibly through a cytotoxic effect on lymphocytes. MMF is an immunosuppressive agent that is increasingly prescribed because it appears to have a more favourable side-effect profile than either cyclophosphamide or cyclosporin. MMF suppresses the growth of T and B lymphocytes through inhibition of inosine monophosphate dehydrogenase, which plays a critical role in the production of DNA of those cells.

We analysed the relationship between the titres of anti-MDA-5 autoantibodies and each cytokine/GF protein concentration before immunosuppressive treatment to find the highest Spearman's rank correlation coefficients in CX3CL1 ($r = 0.8897$, $P < 0.001$) [4]. Serum cytokine/GF protein in this case demonstrated that the concentrations of FGF-2, IL-1ra, IL-17A, IP-10, and MCP-1 decreased after addition of MMF as well as CX3CL1. Besides, eotaxin

and sCD40L increased after addition of MMF. The results suggest that these cytokines/GF may be involved in the development of ILD in ADM with anti-MDA-5 autoantibodies and MMF may be beneficial with the modification of cytokine/GF proteins. Changes in cytokine/GF proteins after addition of MMF should be confirmed in more patients with ADM-ILD.

Disclosure Statements

No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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