Successful rescue treatment of refractory anti-MDA5 autoantibody positive dermatomyositis with rapidly progressive interstitial lung disease using daratumumab

Sirs,

Anti-melanoma differentiation-associated 5 gene autoantibody (anti-MDA5 Ab) positive dermatomyositis (DM) with rapidly progressive interstitial lung disease (RP-ILD) is a severe and difficult-to-treat form of autoimmune myositis with unfavourable 6-month survival rates (1, 2). We report a case of refractory anti-MDA5 DM RP-ILD that improved after daratumumab, a human monoclonal antibody targeting CD38-positive plasma cells.

This study complies with the Declaration of Helsinki. Ethics approval was granted by the Domain Specific Review Board of the National Health Group Singapore (DSRB 2022/00453). Patient consent to participate in this study and for related publication was obtained.

A 30-year-old Chinese man was hospitalised after 3 weeks of intermittent fever, non-productive cough, lethargy, myalgia, and rashes. Physical examination revealed typical DM cutaneous changes and bilateral mid-to-lower zone inspiratory crepitations with no proximal muscle weakness or synovitis. Investigations revealed elevated creatine kinase, C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, ferritin, and neutrophil-to-lymphocyte ratio. Computed tomography thorax showed ground-glass opacities (GGO) with bilateral lower lobe consolidation. Anti-MDA5 Ab signal intensity was strongly positive on EUROLINE Inflammatory Myopathies 16 Ag (IgG) immunoblot assay (LIA) (Euroimmune, Lubeck, Germany).

He was transferred to our centre one week after presentation and intubated on arrival for hypoxemic respiratory failure. Intravenous methylprednisolone (IVMP) 500 mg daily for 3 days, two doses of intravenous rituximab 1g 14 days apart, tofacitinib 5 mg BD, and 6 cycles of plasmapheresis were given on admission. He was successfully extubated after 5 days and discharged 5 weeks later on prednisolone 45 mg daily and baricitinib 2 mg daily (switched from tofacitinib due to transaminitis). However, he was readmitted one week later with worsening dyspnoea and repeat imaging showed worsening bilateral GGO and consolidation. IVMP 500 mg daily for 3 days was repeated. Baricitinib was reverted to tofacitinib as transaminitis had improved. Over the next 4 months, despite continued combination treatment with high dose prednisolone, tofacitinib 5 mg BD, monthly intravenous immunoglobulin for three months, 10 cycles of plasmapheresis and addition of tacrolimus (maximum 2 mg daily), his effort tolerance and hypoxemia continued to worsen. Repeat imaging at month 6 showed worsening GGO with fibrosis. He also remained anti-MDA5 Ab positive on LIA and enzyme-linked immunosorbent assay (ELISA) (3).

At month 6, four weekly doses of intravenous daratumumab 1200 mg (16mg/kg) were given. Oral nintedanib 100mg BD was added at month 7 for progressive lung fibrosis. Four months after daratumumab, he remained stable on prednisolone 12.5mg OM, tofacitinib 5 mg BD, and nintedanib 100mg BD. Anti-MDA5 Ab was persistently undetectable on both LIA and ELISA one month after daratumumab treatment, with improvement in lung function tests and chest radiograph findings (See summary of events in Fig. 1).

This is the third reported case on the successful use of daratumumab in anti-MDA5 DM RP-ILD patients (4, 5). Unlike previous cases, we employed upfront B-cell and autoantibody depletion strategy using rituximab and plasmapheresis. However, this initial strategy was inadequate; sustained serological and clinical remissions in our patient were only achieved after daratumumab.

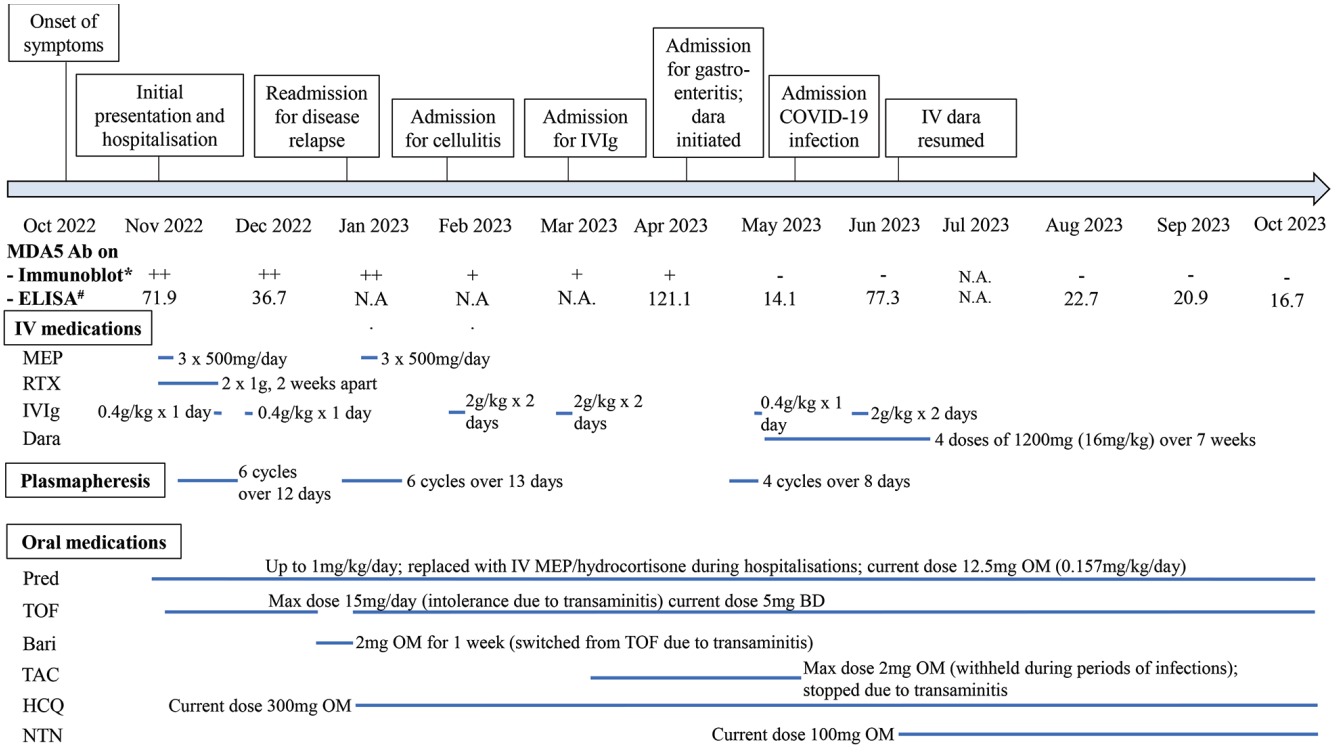

Fig. 1. Treatment and adverse events summary.

*Signal intensity: strongly positive ++; positive +; negative –

#ELISA was performed according to established protocol, normal reference interval ≤30 AU/mL as determined by standard curve generated from pooled anti-MDA5 positive serum samples[3]

Bari: baricitinib; Dara: daratumumab; HCQ: hydroxychloroquine; IV: intravenous; IVIg: intravenous immunoglobulin; MEP: methylprednisolone; NTN: nintedanib; Pred: prednisolone; RTX: rituximab; TAC: tacrolimus; TOF: tofacitinib.

Daratumumab is an anti-CD38 monoclonal antibody licensed for treating multiple myeloma (6). It has been used off-label for treating refractory systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) (7, 8). Besides CD19/20 positive B-cells, CD38-positive long-lived autoantibody-secreting plasma cells are postulated as essential drivers of chronic inflammation in these autoimmune diseases (9).

Interferon (IFN) signatures are up-regulated in the skin, blood vessels and lungs in anti-MDA5 DM RP-ILD (10). Thus, upfront combination therapy to concurrently inhibit type I IFNs secretion, deplete pathogenic autoantibodies produced by autoreactive CD20+ B cells, and block IFN-gamma mediated JAK-1 and JAK-2 activation explains the basis of the methylprednisolone-rituximab-tofacitinib regime with or without plasmapheresis. Anti-CD38 treatment can be considered as novel rescue therapy for high-risk refractory anti-MDA5 Ab positive DM RP-ILD unresponsive to CD20+ B cell depletion. Tyrosine kinase inhibition with nintedanib may retard the progression of lung fibrosis in young high-risk patients.

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