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Interleukin-1 receptor antagonist for refractory anti-MDA5 clinically amyopathic dermatomyopathy

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ABSTRACT

Autoantibodies targeting the melanoma-differentiation-associated gene-5 (MDA5)-encoded ribonucleic acid helicase are associated with clinically amyopathic dermatomyopathy (CADM). Marked systemic inflammation, skin ulcers and severe interstitial lung disease seem frequent. DM treatment consists of immunosuppressants and/or intravenous immunoglobulins, but evidence-based knowledge is lacking. Anakinra (an interleukin-1 receptor antagonist (IL-1RA)) use in this setting has never been reported. Herein, we report on a case of anakinra dramatic and rapid efficacy against general and extramuscular (e.g. calcinosis, arthritis, skin ulcers) in a patient with severe and refractory CADM. Unfortunately, short-term follow-up prevented efficacy evaluation against interstitial lung disease. IL-1RA could be a promising treatment for refractory CADM.

Introduction

Dermatomyositis (DM), an autoimmune connective-tissue disease, usually associates skin, muscle and lung involvements. First described in 2005, autoantibodies targeting the melanoma-differentiation-associated gene-5 (*MDA5*)-encoded ribonucleic acid helicase are associated with clinically amyopathic dermatomyopathy (CADM) (1). To our knowledge, <100 anti-MDA5-CADM patients have since been reported. Marked systemic inflammation, skin ulcers and severe interstitial lung disease are apparently frequent in CADM (2, 3). DM treatment consists of immunosuppressants and/or intravenous immunoglobulins (IVIg), but evidence-based knowledge is lacking (4). Anakinra (an interleukin-1 receptor antagonist (IL-1RA)) use in anti-MDA5 CADM has never been reported.

Case report

A 53-year-old woman was diagnosed with CADM based on fever with high blood inflammation, lilac rash on the upper eyelids, Gottron's papules, skin biopsy containing perivascular lymphocytic infiltrates, severe calcinosis, skin ulcers and polyarthritis, without muscle symptoms or elevated muscle enzymes. Extensive infectious, autoimmune (anti-nuclear, -Jo1, -PL7, -PL12, -EJ -OJ, -KS, -SRP, -RNP, -PM-SCL, -Ku, -TIF1γ and -Mi2 serologies) and cancer (whole-body computed tomography scan, digestive endoscopies) work-ups were negative. At referral (11/2010) to our institution, previously prescribed treatments (prednisone, hydroxychloroquine, methotrexate, azathioprine, IVIg and 1 rituximab infusion) had been responsible for numerous side effects: cytomegalovirus viremia, methicillin-resistant *Staphylococcus aureus* bacteraemia, left-lung pneumonia, toxoplasma uveitis and severe denutrition (30 kg lost over 2 years). The patient became bedridden and active disease persisted: prolonged fever and elevated inflammatory markers, despite negative infectious workup, worsening skin ulcers (Fig. 1A), new painful calcinoses requiring high-dose morphine and interstitial pneumonia onset. Her positron-emission tomography (PET) scan showed high standardised fluorodeoxyglucose-uptake values in skin calcinoses (Fig. 2A and C). Because of her rapid deterioration, prednisone was quickly tapered (to 5 mg/day), azathioprine and rituximab were stopped, while IVIg (2 g/kg/month) and methotrexate (oral 15 mg/week) were continued.

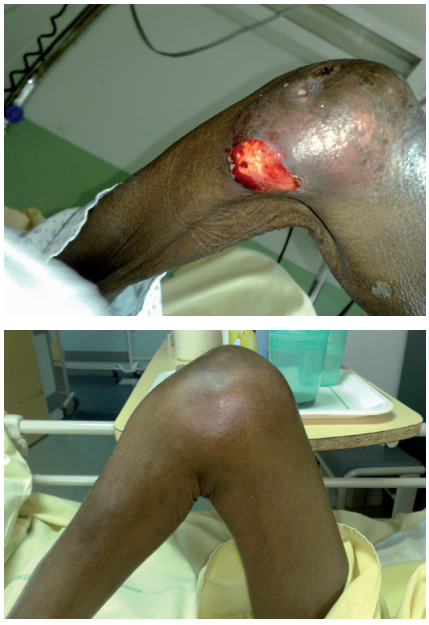

Fig. 1. Right knee ulcer before (**A**) and 4 weeks after (**B**) starting anakinra.

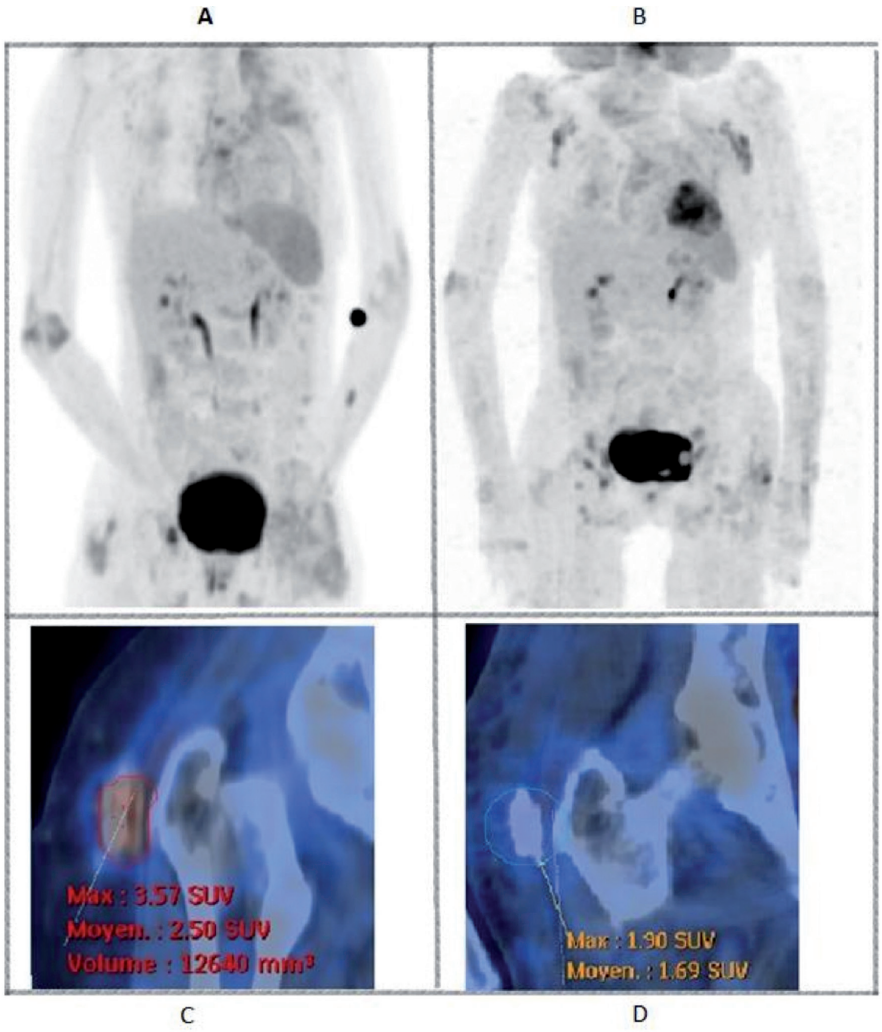

Fig. 2. Positron emission tomography with [^{18}F]-fluorodeoxyglucose (FDG) integrated with computed tomography before (**A**, **C**) and 4 months after (**B**, **D**) starting anakinra in maximum-intensity-projection (**A**, **B**) and coronal fused (focused on the gluteus maximus muscle) (**C**, **D**) images showing in the latter a 46% standardised uptake value reduction (delta SUV max).
Acquisition from the base-skull to the base-thigh one hour after injection of 2.5 MBq/kg of FDG. Glucose levels were normal and comparable for the two exams (4 mmol/l).

In April 2011, colchicine prescribed for right knee calcium-pyrophosphate-crystal monoarthritis was transiently effective against joint inflammation and general symptoms. This led us to use subcutaneous anakinra (100 mg/day) salvage therapy which indeed achieved fast and dramatic improvement: fever dropped, calcinosis nodules diminished, pain abated, skin ulcers healed (Fig. 1B), C-reactive protein fell (179 to 31 mg/L in 8 days) and serum albumin rose (22 to 32 g/L in 1 month). The PET scan 4 months after starting anakinra showed quasi-complete calcinosis-hypermetabolism regression (Fig. 2B and D). She died suddenly 5 months later of aspiration pneumonia. Postmortem serum analysis was anti-MDA5-positive.

Anakinra was effective in a mouse model of inflammatory myopathy (5), a patient with anti-Jo1 myopathy (6) and a recent series including DM and polymyositis patients (7). Indeed, blocking IL-1 reduces major histocompatibility complex-I ligand, CD40, inducible T-cell costimulator-l ligand and intercellular cell-adhesion molecule-1 expression by myofibres, thereby diminishing T-cell activation (8). Lastly, anti-MDA5 antibodies potentially causing innate immune-response dysregulation (leading to macrophage activation and a cytokine storm) (9) supports IL-1 pathway blockage in anti-MDA5 CADM.

Our case suggests that anakinra could be a promising treatment for refractory CADM-associated systemic inflammation and/or extramuscular symptoms (*i.e.* skin ulcers and calcinosis). Unfortunately, short-term follow-up prevented efficacy evaluation against interstitial lung disease. Future clinical and fundamental studies are needed to confirm these preliminary observations.

Acknowledgements

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References

1. SATO S, HOSHINO K, SATOH T *et al.*: RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. *Arthritis Rheum* 2009; 60: 2193-200.
2. SONTHEIMER RD: Clinically amyopathic dermatomyositis: what can we now tell our patients? *Arch Dermatol* 2010; 146: 76-80.
3. CERIBELLI A, FREDI M, TARABORELLI M *et al.*: Prevalence and clinical significance of anti-MDA5 antibodies in European patients with polymyositis/dermatomyositis. *Clin Exp Rheumatol* 2014; 32: 891-7.
4. DALAKAS MC: Immunotherapy of myositis: issues, concerns and future prospects. *Nat Rev Rheumatol* 2010; 6: 129-37.
5. SUGIHARA T, OKIYAMA N, WATANABE N, MIYASAKA N, KOHASAKA H: Interleukin-1 and tumor necrosis factor α blockade treatment of experimental polymyositis in mice. *Arthritis Rheum* 2012; 64: 2655-62.
6. FURLAN A, BOTSIOS C, RUFFATTI A, TODESCO S, PUNZI L*:* Antisynthetase syndrome with refractory polyarthritis and fever successfully treated with the IL-1 receptor antagonist, anakinra: a case report. *Joint Bone Spine* 2008; 75: 366-7.
7. ZONG M, DORPH C, DASTMALCHI M *et al.*: Anakinra treatment in patients with refractory inflammatory myopathies and possible predictive response biomarkers: a mechanistic study with 12 months follow-up. *Ann Rheum Dis* 2014; 73: 913-20.
8. GHERARDI RK: Pathogenic aspects of dermatomyositis, polymyositis and overlap myositis. *Presse Méd* 2011; 40: e209-18.
9. NAKASHIMA R, IMURA Y, KOBAYASHI S *et al.*: The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. *Rheumatology* (Oxford) 2010; 49: 433-40.