Pediatric Rheumatology

LETTER TO THE EDITOR Open Access

Successful treatment of an anti-MDA5 antibody-positive Juvenile Dermatomyositis patient with refractory interstitial lung disease using tofacitinib

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Juvenile dermatomyositis (JDM) is a rare autoimmune disorder affecting children, mainly characterized by skin rash and muscle weakness [1]. Anti-MDA5 antibody-positive JDM represents a distinct disease phenotype with a high risk of developing life-threatening progressive interstitial lung disease (ILD) [2]. The pivotal role of the type I interferon (IFN) pathway in the pathogenesis of anti-MDA5 positive JDM has prompted the exploration of Janus kinase (JAK) inhibitors as a therapeutic option [3]. Nevertheless, while the efficacy and safety of JAK inhibitors have been established in clinical trials including adult-onset anti-MDA5-antibody positive DM [4], evidence in paediatric cases with progressive or refractory ILD is limited. In this report we describe the efficacy and safety of tofacitinib, a JAK 1/3 inhibitor, in treating an anti-MDA5-positive JDM young girl with refractory ILD, highlighting the potential of JAK inhibitors as targeted therapy in these patients.

A previously healthy 7-year-old female patient of Caucasian ethnicity presenting with a 6-month history of fatigue, weight loss, skin lesions (Fig. 1A-B), and mildly impaired muscle strength was diagnosed with anti-MDA5 positive JDM. JDM-associated ILD was also detected during the initial diagnostic workup (Fig. 2A). Initial treatment with methylprednisolone pulses followed by high-dose intravenous glucocorticoids, oral cyclophosphamide and monthly intravenous immunoglobulin (IVIG) infusions led to skin (Fig. 1C-D) and muscle disease remission, but failed to halt lung disease progression (Fig. 2B). Supported by reports on adult-onset DM [5] and the presence of elevated peripheral blood type I interferon gene signature (IGS) based on the expression of six type I IFN-related genes (*IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2*, *SIGLEC1*) in the patient (Fig. 3), tofacitinib in combination with subcutaneous methotrexate and IVIG was initiated. This treatment led to a stable remission, near-complete resolution of the pulmonary involvement (Fig. 2C-D), discontinuation of glucocorticoids and normalization of peripheral blood type I IGS

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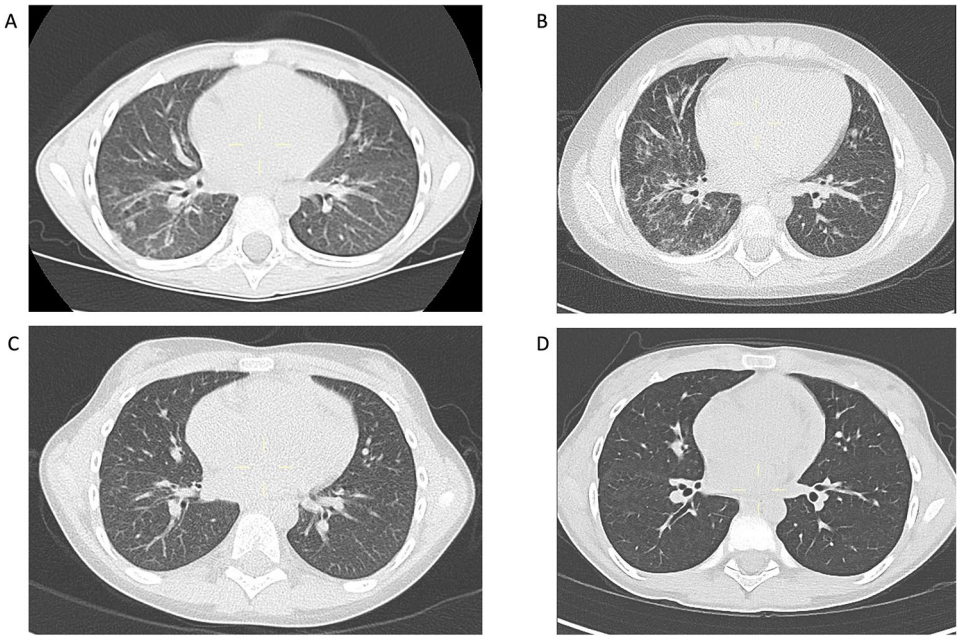

Fig. 1 Temporal progression of pulmonary features on lung High-Resolution Computed Tomography (HRCT), axial view. **A**) Lung HRCT scan performed at disease onset showing small peri-bronchial consolidations in the apical segment and subpleural region of the posterior basal segment of the right lower lobe, with additional small peripheral consolidations in the posterior segment of the right upper lobe. **(B)** Lung HRCT performed four months after oral cyclophosphamide initiation and before tofacitinib therapy, showing persistent thickening of the intralobular and interlobular interstitium with reduced density and less consolidation compared to the previous scan (apical and posterior segments of the upper lobe, all segments of the lower lobe, and the lateral segment of the middle lobe) in the right lung; peri-bronchial interstitial thickening in the peri-hilar region; a small hyperdense area is observed in the anterior segment of the left upper lobe (subpleural). **(C)** Lung HRCT performed six months after tofacitinib initation, demonstrating nearly complete resolution of the pathological findings, showing a residual area of mild subpleural ground-glass opacity on the right lobe. **(D)** Lung HRCT performed two years after tofacitinib initiation, revealing minimal ground-glass opacity in the subpleural region of the right upper lobe, mild septal, pleural and interlobular septal thickening at the apices

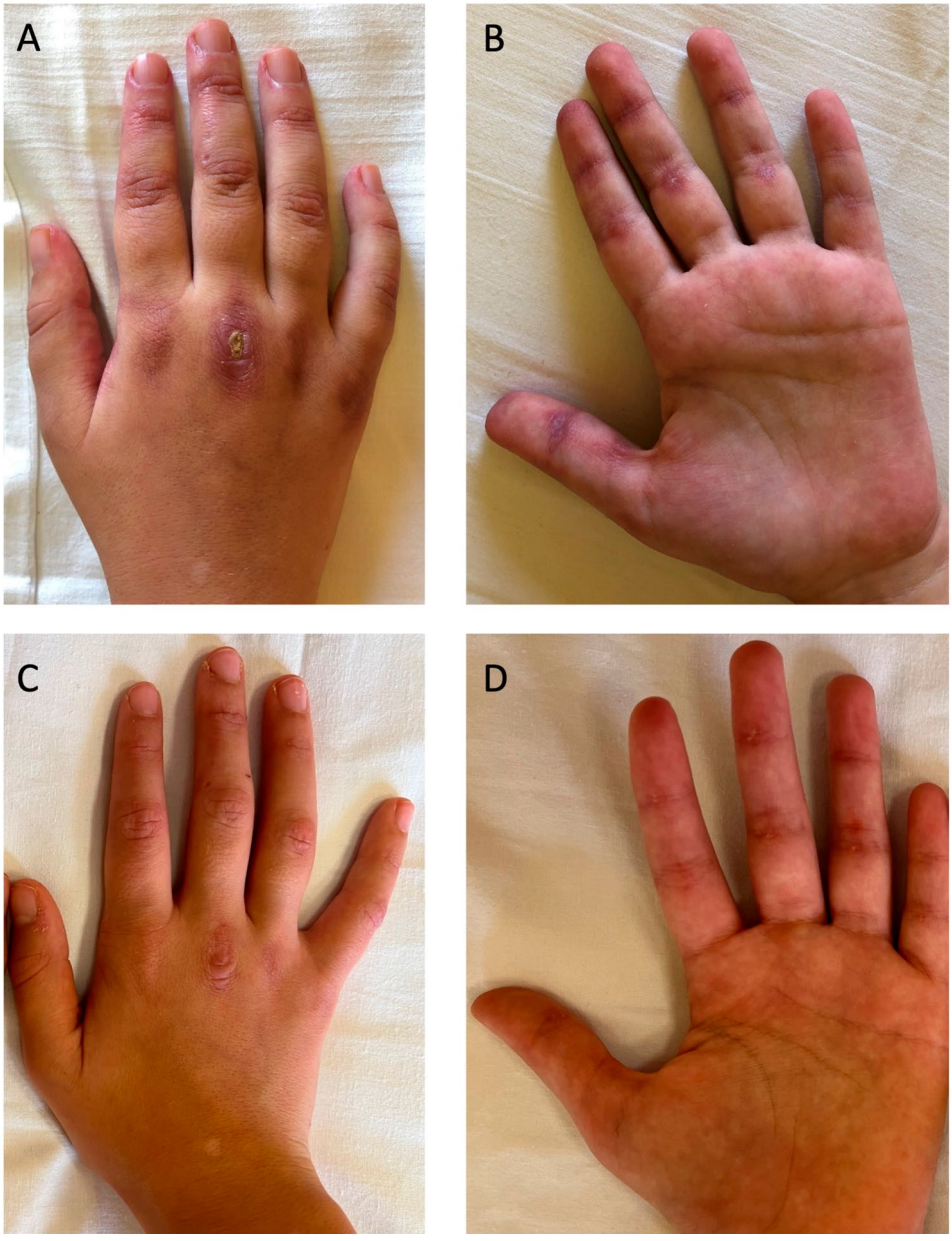

Fig. 2 Skin involvement at first admission to our department (pre-tofacitinib treatment) (**A**-**B**) and eighteen months after tofacitinib initiation **(C-D). (A)** Gottron's papules and scar tissue from previous skin ulcerations on the dorsal surface of the right hand. **(B)** Gottron's inverse papules on the palmar surface of the left hand. Resolution of skin involvement eighteen months after tofacitinib initiation on the dorsal surface of the right hand **(C)** and the palmar surface of the left hand **(D)**

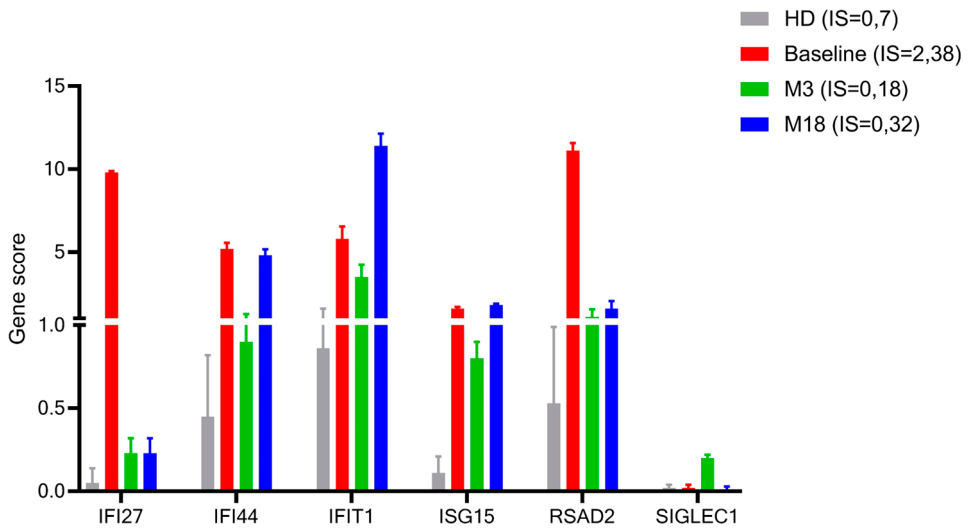

Fig. 3 The Interferon gene signature (IGS) based on the expression of six type I IFN-related genes (*IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2*, *SIGLEC1*) on peripheral blood throughout the disease course. Before the initiation of tofacitinib therapy, a positive type I IGS was observed. Three months after tofacitinib initiation, the IGS turned negative. Eighteen months after starting tofacitinib, the IGS was stably negative, but a mild increase in the expression of *IFI44L*, *IFIT1*, and *RSAD2* was observed. The IGS was assessed by calculating the expression of six type I interferon-stimulated genes (ISGs) (IFI27, IFI44L, IFIT1, ISG15, RSAD2, and SIGLEC1). Real-Time PCR was performed using gene-specific custom-designed FAM probes (TibMolBiol, Roche, Germany) in duplicate. Gene copy number were calculated as follow: (1) standard curves were prepared for each gene with 10-fold serial dilutions of the synthetic control; (2) curves were generated through linear regression analysis. Values were normalised with the geometric means of two internal controls (TBP and HPRT1) and expressed as gene score (GS). IFN Score (IS) was calculated as the geometric mean of the GS of the six ISGs. The IS cut-off value was determined based on 26 healthy donors (HD) using the mean + 2 standard deviations of their GS to classify as positive/negative the IS analysis (normal IS values < 0.7). HD normal reference values and standard deviation for each gene are reported in the graph (in grey). The bar blot illustrates gene scores on the y-axis, with individual genes listed on the x-axis. Coloured bars represent the patient (red for baseline, green and blue for three and eighteen months after tofacitinib initiation, respectively), while grey bars represent HD

(Fig. 3). No adverse effects were observed during two-year follow-up evaluations.

This case underscores the promising efficacy and safety of tofacitinib in managing anti-MDA5-positive JDM with ILD non-responsive to aggressive conventional immunosuppressive treatments. It also emphasizes the importance of early intervention and the potential benefits of employing targeted therapies based on specific biomarkers such as the type I IGS. Future research should focus on the design of international randomized controlled trials aimed to assess the efficacy and safety of JAK inhibitors in JDM, to foster personalised treatment approaches and improve patient outcomes.

Abbreviations

DM	Dermatomyositis
IFN	Interferon
IGS	Interferon Gene Signature
ILD	Interstitial Lung Disease
IS	Interferon Score
IVIG	Intravenous Immunoglobulin
JAK	Janus Kinase
JDM	Juvenile Dermatomyositis
MDA5	Melanoma Differentiation-Associated protein 5

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Author contributions
VN contributed to the conception of the study, collected clinical and radiological data, and wrote the first draft of the manuscript. SP and AIRG contributed to data collection. PB performed the type I IFN signature assays. MCC, RB, RC, SV, RP, AC, MG, AR provided critical input during the manuscript drafting and critically reviewed the final version of the manuscript. SR supervised the project, significantly contributed to the conception of the study and critically reviewed the manuscript throughtout the drafting process. All authors read and approved the final version of the manuscript.

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Data availability
Data used during the current study are available from the corresponding author SR on reasonable request.

Declarations

Ethical approval
The off-label use of tofacitinib was approved by the local ethics committee ("Comitato Buon Uso del Farmaco") of the IRRCS Giannina Gaslini.

Consent for publication
Written informed consent for publication of their clinical details and/or clinical images was obtained from the parent of the patient. A copy of the consent form is available for review by the Editor of this journal.

Competing interests
VN, SP, AIRG, PB, SR have no competing interests. CMC, SV and RP received speaker fee from SOBI. RC received speaker fee from Sobi and Novartis,

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