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Short communication

Successful treatment of extensive calcifications and acute pulmonary involvement in dermatomyositis with the Janus-Kinase inhibitor tofacitinib – A report of two cases

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A B S T R A C T

Introduction: Dermatomyositis (DM) can be complicated by calcinosis and interstitial lung disease (ILD). Calcinosis can be severely debilitating or life-threatening and to date there is no treatment with proven efficacy. In DM type I interferon contributes to pathophysiology by inducing the expression of proinflammatory cytokines and the JAK-STAT (signal transducer and activator of transcription) pathway may be involved in the regulation of mitochondrial calcium store release, a process potentially important for calcification in DM. JAK-inhibition may therefore be an attractive therapy in DM complicated by calcifications.

Methods and results: We report on the fast and persistent response of extensive and rapidly progressive DM-associated calcifications in two patients treated with the JAK-inhibitor tofacitinib. During the 28-week observation period in both patients no new calcifications formed and existing calcifications were either regressive or stable. Furthermore, concomitant life-threatening DM-associated ILD (acute fibrinous and organizing pneumonia; AFOP) in one patient rapidly responded to tofacitinib monotherapy. Both patients were able to taper concomitant glucocorticoids. Tofacitinib was well tolerated and safe.

Conclusions: The results of our study support the role of JAK/STAT signaling in the development of calcinosis and ILD in DM. Tofacitinib may be an effective and safe treatment for calcinosis in DM and potentially for other connective tissue disease complicated by calcinosis.

1. Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) characterized by muscular inflammation, skin involvement and frequent systemic manifestations. The broad spectrum of systemic manifestations comprises vasculopathy, interstitial lung disease (ILD), muscular, and (sub)cutaneous calcifications. Calcinosis occurs in up to 20% of adult DM-patients and is characterized by deposition of insoluble calcium salts [1,2]. Calcinosis in DM can lead to extensive functional disability, intense pain and infectious complications. The pathogenesis of insoluble calcium-phosphate deposition may involve vascular and inflammatory mechanisms. In DM it is hypothesized that mitochondrial calcium stores in muscle cells are released during the inflammatory muscular process [1,2]. Furthermore, changes in calcium-phosphate solubility and mitochondrial damage have been proposed as pathomechanisms [1,3–6]. Long disease duration is a predictive factor for calcinosis in DM [1]. With increasing immunemodulatory treatment options the long-term outcome of IIM improved considerably and 10-year survival rate exceeds 90%. Nevertheless, to date there is no effective treatment available for calcinosis. Immunomodulatory therapies, calcium channel blockers, bisphosphonates, aluminium hydroxide and others failed to prove efficacy [1]. ILD, most frequently of the nonspecific interstitial pneumonia subtype, is a further therapeutic challenge in DM. Other less frequent pulmonary manifestations of DM have been described [7,8]. Acute fibrinous and organizing pneumonia (AFOP) is a very rare pulmonary disorder with only few reported cases, a very variable outcome and no established treatment regimen [9–13]. In anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive DM rapidly progressive ILD has been reported [14]. Recently, Janus-Kinase inhibitors (JAK-I) have been successfully introduced into the treatment armamentarium of autoimmune and inflammatory diseases, but data on their application in DM

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are scarce. In DM type I interferon contributes to pathophysiology by inducing the expression of proinflammatory cytokines and the JAK-STAT (signal transducer and activator of transcription) pathway is involved in cutaneous manifestations of DM [15]. Additionally, overexpression of STAT1 in muscle tissue of DM-patients has been reported [16,17]. Furthermore, STAT3 is able to translocate into mitochondria and may be involved in the regulation of mitochondrial calcium store release, a process potentially important for calcification in DM [18,19]. Based on these findings JAK-I that are able to interfere with recruitment of STATs and to downregulate type I and II cytokine signaling, seem an attractive therapy in DM. Nevertheless, data on safety and efficacy of JAK-I in DM are insufficient, and there is no information on their effect on calcifications in DM. We report two patients with severely calcifying, autoantibody-positive dermatomyositis treated with the JAK-I tofacitinib. One of the patients additionally suffered from severe, life-threatening AFOP.

2. Methods

Information on disease course, immunosuppressive treatment and laboratory parameters were extracted from the patients' database of the Clinic for Rheumatology and Clinical Immunology, University Medical Center Freiburg. The study was approved by the local ethics committee of the University Hospital Freiburg and both patients provided written informed consent (FR: 507/16). The work described has been carried out in accordance with the Declaration of Helsinki. Anti-nuclear antibody (ANA) staining pattern was assessed by indirect immunofluorescence on 2100-Ro HEp-2000® cells (Fluorescent ANA-RoTest System, Immuno Concept, Sacramento, CA, USA). Screening for autoantibodies was done by enzyme-linked immunosorbent assay (ELISA) using ANA-Profile 3 (EUROIMMUN AG, Luebeck, Germany). Antibodies against double stranded deoxyribonucleic acid (DNA) were detected using dsDNA IgG ELISA (Diagnostica AB, Malmö, Sweden). Screening for myositis autoantibodies was done by euroline myositis profile 4 (EUROIMMUN AG, Luebeck, Germany).

3. Results

Patient A is a 54 year-old female. At the age of 40 she presented with moderate, bilateral myalgia and weakness of the proximal extremity musculature. She had Gottron papules above the volar metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints and nailfold changes with giant capillaries. Creatine kinase (CK) was slightly elevated. The patient was diagnosed with inflammatory myopathy and treated with prednisone (initially 1 mg/kg body weight, tapered to 5 mg/day maintenance dose). Myalgia improved on prednisone therapy and CK concentrations normalized. Three years after first manifestation of myopathy calcifications at the third distal interphalangeal joint (DIP) of the right hand and the second DIP of the left hand developed. Because of slowly progressive calcifications she was treated with bisphosphonates, sevelamer-carbonate, aluminium-hydroxide and amlodipine without any effect.

Twelve years after first diagnosis of myositis proximal myalgia recurred together with partly immobilizing bilateral arthritis of the hips and knees. CK was slightly increased to 204 U/L. Contrast medium enhanced magnetic resonance imaging (MRI) of the pelvis and the proximal femoral region showed edema of the extensor, adductor and gluteal muscles with contrast medium uptake. ANA immunofluorescence was positive with detectable anti-Mi2 and anti-Ro52 autoantibodies. Dermatomyositis was diagnosed ([20]). At that time muscular and subcutaneous calcifications had become rapidly progressive and were most pronounced at both hands, where they were resulting in almost complete functional disability. Further extensive calcifications were found at the buccal and paranasal area, the left elbow, the gluteal region, the right thigh, both knees and adjacent to the right shinbone (Fig. 1 A-H, Table 1). Extensive calcifications of both hands partly extruding to the skin resulted in frequent infectious complications (phlegmon, abscesses) that required in sum 10 surgical interventions with hospitalization. Treatment with methotrexate (15 mg/week) improved muscular symptoms but was not able to prevent the rapid progression of calcifications (Fig. 1A–H). Therefore, tofacitinib therapy (5 mg twice daily) was started in combination with methotrexate (12.5 mg/week) and prednisone (5 mg/day). Bilateral arthritis of hips and knees resolved after one week of treatment. At that time inflammation adjacent to calcifications had started to decrease. After two weeks of tofacitinib treatment no new calcifications developed and existing calcifications did not augment. After four weeks of tofacitinib therapy the patient reported that some calcifications had started to shrink. The successive reduction of calcifications was accompanied by an improvement in the functional status of the patient. Health assessment questionnaire-disability index (HAQ-DI) decreased from 2.15 (severe to very severe disability) before start of tofacitinib to 1.38 (mild to moderate disability) after 16 weeks and 0.85 after 28 weeks of tofacitinib therapy (Fig. 1 I). After 28 weeks the patient reported a further improvement of her general condition. Inflammation of calcifications had completely resolved, and calcifications were either stable or regressive (Table 1). Acral ulcers had disappeared and the functional manual status had further improved. Arthritis remained in complete remission and Raynaud's phenomenon had completely resolved. Apart from a moderate and transient hypercalcemia and an increase in body weight (Table 1) no side effects occurred during tofacitinib treatment.

Patient B is a 55 year-old female. At age 54 she suffered from night sweats and fever, severe hoarseness, dysphagia, myalgia with a moderate general muscle weakness of the proximal musculature and skin involvement. She had heliotrope rash of the upper chest, back and upper extremities and Gottron papules. She complained of painful calcifications at multiple localizations (Table 1) accompanied by polyarthralgia and bilateral carpitis. Furthermore, she reported dyspnea on exertion. Myoglobin was slightly increased and anti-MDA5-antibodies were detected. MRI showed symmetrical, muscular contrast-medium enhancement and muscle biopsy was compatible with dermatomyositis (Table 1) ([20,21]). Pulmonary function tests (PFTs) at the time of diagnosis showed a restrictive lung function defect. Diffusion capacity was severely reduced and total lung capacity (TLC) and forced vital capacity were moderately reduced. Computed tomography (CT) showed peripheral reticulations and consolidation consistent with DM-associated ILD. The patient was refractory to treatment with azathioprine, hydroxychloroquine, mycophenolate mofetil, tacrolimus, and intravenous immunoglobulins in combination with high-dose glucocorticoids and did not tolerate methotrexate. Within four weeks the patient's pulmonary function deteriorated and severe dyspnea required hospitalization for non-invasive ventilation therapy. PFTs showed severe hypoxemia, increasing restriction and decreasing diffusion capacity. A positron-emission tomography (PET)-CT scan revealed diffuse hypermetabolism of the pulmonary parenchyma and ground glass opacities. Cryobiopsy showed an organizing pneumonia with focal intraalveolar fibrin exudates and distinct activation of alveolar epithelia (supplementary figure 1) compatible with acute fibrinous and organizing pneumonia (AFOP). Together with deterioration of pulmonary function skin involvement exacerbated and painful, subcutaneous calcifications increased substantially. Immunosuppressive treatment was changed to cyclosporine, rituximab and glucocorticoids (150 mg prednisolone/day). Subsequently, pulmonary function stabilized and pulmonary infiltrates decreased, but the patient remained dependent on continuous oxygen supply (1 L/min) (Fig. 2 B). Calcifications were completely refractory to treatment. Despite of continued rituximab/cyclosporine-therapy and depleted B cells the patient's condition worsened during follow-up. Dyspnea and oxygen-dependency increased (continuous oxygen supply 2 L/min) and calcifications as well as skin involvement progressed, leading to repeated hospitalization. Eight months after first rituximab application treatment was changed to

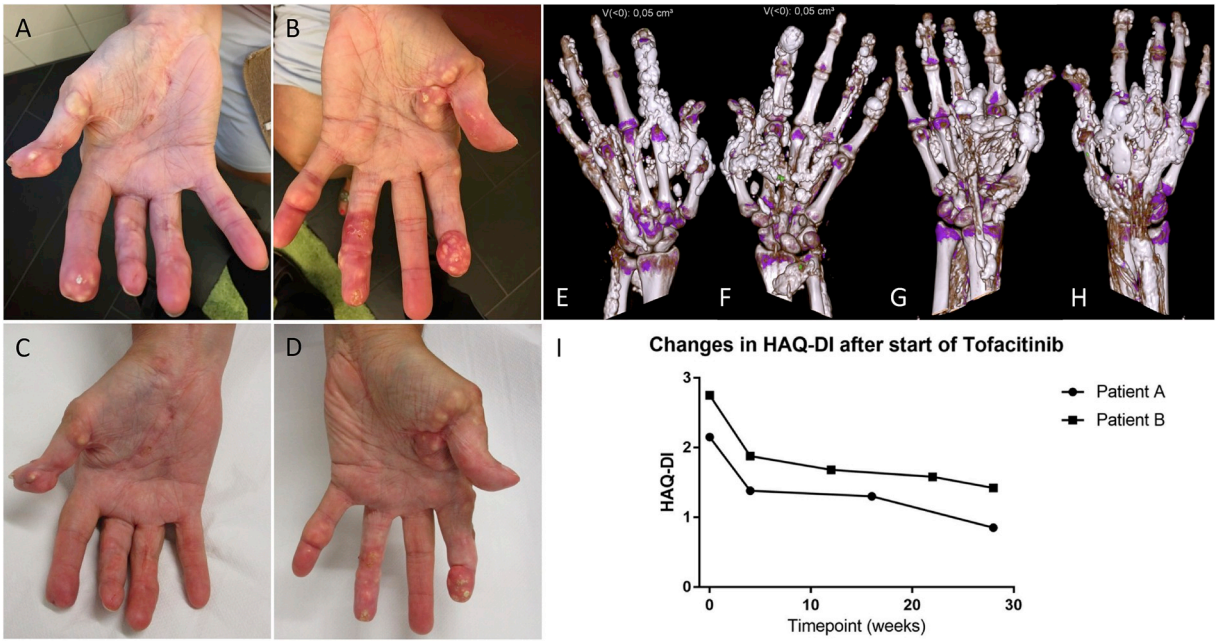


Fig. 1. Extensive calcifications with local inflammation at the right (A) and left (B) hand of patient A before start of tofacitinib treatment. Decreasing inflammation and calcifications after 16 weeks of tofacitinib treatment (C and D). Dual energy computer tomography showed extensive soft tissue calcifications ((E) left hand volar, (F) left hand palmar, (G) right hand volar, (H) right hand palmar). Decrease in HAQ-DI in both patients during tofacitinib treatment (I).

tofacitinib monotherapy (5 mg twice/day). Pulmonary, skin and muscular-skeletal symptoms responded rapidly. Five days after start of tofacitinib dyspnea started to decrease, the intense abdominal pain due to calcifications improved, and polyarthralgia and carpitis were in remission. After twelve weeks the general condition had ameliorated considerably (Fig. 1 I). PFTs revealed an increase in peak flow, inspiratory muscle strength and diffusion capacity (Fig. 2 D, E). Only minimal pulmonary infiltrates remained (Fig. 2 C), and the patient was no longer dependent on therapeutical oxygen. Cutaneous dermatomyositis disease area and severity index (CDASI version 2; activity section) had declined from 25 before treatment to 10. The patient reported regressive calcifications at the abdomen, the left upper arm and the left thigh. Abdominal CT-scan showed slightly thinned periumbilical calcifications without formation of new calcifications (Fig. 2 F, GI). Severe hoarseness had almost completely resolved and general muscular strength had increased. Twenty-eight weeks after start of tofacitinib the patient reported further improvement (Fig. 1 I). She was able to climb four floors and swim 2000 m without stopping. PFTs revealed a further improvement in TLC and respiratory muscle strength (Fig. 2 D, E). The 6 min walking test had almost normalized (PaO2 75 mmHg before and 70 mmHg after 411 m; walking distance before tofacitinib 270 m). CDASI had declined to three. She reported that no new calcifications had formed, some calcifications had even further improved, while others remained unchanged (Table 1). No side effects occurred during tofacitinib treatment except for an increase in bodyweight (Table 1).

4. Discussion

Dermatomyositis is frequently complicated by systemic manifestations. We described two patients that suffered from severe, debilitating calcinosis. To date no therapy has proven to be efficacious in the treatment of DM-associated calcinosis [1,2]. Early aggressive treatment of juvenile DM has been associated with a lower incidence of calcinosis [2] potentially pointing towards an inflammation driven process of calcification. Tofacitinib, a relatively unspecific JAK-I targets multiple proinflammatory cytokines, important in the pathogenesis of DM [15,16] and affects phosphorylation of different STATs including STAT1 and STAT3. There are few case reports and small case series reporting on the use of JAK-I in dermatomyositis [14,22–24], but to date there is no data on safety and efficacy of JAK-I in DM complicated by calcinosis. In both patients tofacitinib treatment was able to stop rapidly progressive calcifications in all locations. The treatment response of the inflammatory changes accompanying cutaneous calcifications was rapid within few weeks. Furthermore, several calcifications started to shrink and some completely disappeared after 28 weeks of tofacitinib treatment. To date the pathogenesis of insoluble calcium-phosphate deposition in DM is not completely clear but dysregulated mitochondrial calcium storage/release may be involved [19]. The JAK-STAT3 signaling pathway is regulating nuclear transcription after activation of cognate receptors by cytokines and growth factors. Additionally, there are non-canonical and non-genomic activities of STAT3 [18] and STAT3 may be involved in the regulation of mitochondrial calcium store release, a process important for calcification in DM [19]. By interfering with proinflammatory cytokine signaling and STAT3 phosphorylation tofacitinib may potentially target two of the mechanisms relevant for calcifications in dermatomyositis [25]. We treated one patient in combination with methotrexate, while the other received tofacitinib monotherapy. As in both patients calcifications improved, it remains unclear, whether the combination therapy is more effective. A tendency to a faster response of calcifications with the combination therapy was observed, hence combining tofacitinib with methotrexate might be advantageous. Tofacitinib was well tolerated and no treatment-related adverse events occurred except for a transient hypercalcemia in one patient and an increase in bodyweight (despite of a reduction of the glucocorticoid dosage) in both patients. Even in patient B that was previously treated for severe concomitant ILD with multiple immunosuppressants no infectious complications arose during tofacitinib therapy. ILD is relatively common in dermatomyositis and non-specific interstitial pneumonitis (NSIP) is the most frequent subtype [7,8]. In patient B DM was complicated by AFOP, a very rare entity of ILD, with to date no reported case in adult DM [9]. The clinical course of AFOP is very variable, but can be rapidly progressive with fatal outcome [9–13]. Patient B was MDA5-positive and a rapid ILD course has been reported in MDA5-positive DM [14]. Indeed, patient B showed rapid deterioration of pulmonary function and was refractory to various

Table 1

	Patient A	Patient B
Baseline characteristics		
Sex	Female	Female
Age at TOF start (y)	54	55
Disease duration (y)	15	1
Smoking status	no	stopped 10 y before start of tofacitinib
Autoantibodies		
ANA-pattern IIF	Positive, homogenous nuclear pattern, Titer 1:100	Positive, homogeneous to fine-speckled pattern, Titer 1:1600
ENA-profile	anti-Ro52 positive	anti-Ro52 positive, DFS70 positive
MSA	anti-Mi2 positive	anti-MDA5 positive
Tissue biopsies		
Skin	Calcinosis cutis	Dermatomyositis with calcification
Muscle	not done	M. soleus: perivascular and perifascicular inflammation with T helper cells, B cells and macrophages; C5b9-deposition;
Lung	not done	AFOP
Imaging		
MRI	Myositis in extensor and adductor muscles of the leg, and M. quadriceps femoris	Myositis in M. iliopsoas, gluteal muscles, ischio-crural muscles and right M. soleus
Prior treatment		
Glucocorticoids	5–10 mg/day	15 mg/day
Calcium antagonists	Amlodipine	Amlodipine
NSAR	Ibuprofen	none
Bisphosphonates	Etidronate	Ibandronate
sDMARDs and bDMARDs	Methotrexate 12.5 mg/week	Methotrexate, Azathioprine, Tacrolimus, Hydroxychloroquine, IVIG, Cyclosporine, Rituximab (2 × 1 gram),

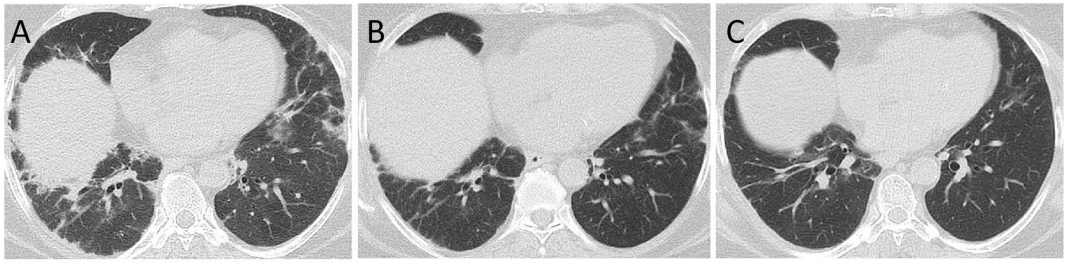
Treatment with tofacitinib

	Patient A		**Patient B**	
	Prior to tofacitinib	After 28 months	Prior to tofacitinib	After 28 months
BMI (kg/m^2)	31.6	36.51	30.86	38.10
Skin manifestation				
Facial erythema	no	no	yes	no
Heliotrope rash	no	no	yes	very subtle
Gottron's papules	yes	no	yes	no
Raynaud's phenomenon	yes	no	yes	improved
Fingertip ulcers	yes	no	yes	no
Nailfold changes	megacapillaries	not done	megacapillaries	not done
Calcification				
Involved tissues	Skin, muscle, subcutaneous tissue		Skin, muscle, subcutaneous tissue	
Localizations of extensive calcifications:	1. Both hands	1. Improved	1. Abdominal adipose tissue	1. Improved
	2. Forearms	2. Improved	2. Left gluteal region	2. Stable
	3. Face	3. Improved	3.left upper arm	3. Improved
	4. Gluteal region	4. Improved	4. Left forearm	4. Stable
	5. Thighs	5. Stable	5. Both elbows	5. Improved
	6. Knees	6. Stable	6. Right shinbone	6. Improved
	7. Shinbone	7. Stable	7. Left thigh	7. Sligthly improved
	8. Left elbow	8. Stable		
Organ manifestation				
Arthritis	Hip, knee bilateral	resolved	Hip, carpus bilateral	resolved
Lung	Normal chest CT, normal PFT	Normal PFT	Severe dyspnea, O2-dependent	Normalization of pulmonary function
GI-tract	no	no	Dysphagia	improved
Heart	no	no	Congestive heart failure	Normalization of heart function
Laboratory results				
CK (U/L)	350*, 114**	154	76*,39**	112
Myoglobin (ng/mL)	not done	46	76*,38**	36
CRP (mg/L)	11.2	7.94	12.9	12.7
Ferritin (ng/mL)	307*, 83**	110	674*,102**	30
ProBNP (pg/mL)	88	not done	214	< 50
Calcium (mmol/L)	2.43	2.43	2.35	2.39

Abbreviations: AFOP Acute fibrinous and organizing pneumonia, BMI body mass index, CK creatine kinase, CRP C-reactive protein, CT computed tomography, GI gastrointestinal, IVIG intravenous immunoglobulin, MSA myositis specific antibody, PFT pulmonary function tests, TOF tofacitinib, VAS visual analogue scale, y year, * at diagnosis, ** prior to start of tofacitinib. Normal range: ferritin 15–150 ng/mL, myoglobin 19–51 ng/mL, CK < 170 U/L, calcium 2.15–2.50 mmoL/l, CRP < 5 mg/L.

immunosuppressants. The combination of rituximab and cyclosporine led to an only transient and partial stabilization of the patient's pulmonary function and had no effect on calcinosis. After initiation of tofacitinib in patient B pulmonary, skin and muscular-skeletal manifestations improved rapidly. Five patients with MDA-positive DM and refractory interstitial lung disease treated with tofacitinib in combination, cyclosporine and cyclophosphamide have been reported [14]. While three patients improved, two patients died, and all patients suffered from severe infectious adverse events. While the subtype of ILD has not been defined in this study and patients had more poor prognostic factors, the favorable outcome of our patient may indicate that tofacitinib can be effective even when used as monotherapy in DM-ILD.

In conclusion, our study supports the role of JAK/STAT signaling in the development of calcinosis and ILD in DM. Tofacitinib may be an effective and safe treatment for calcinosis in DM and potentially for other connective tissue disease complicated by calcinosis.



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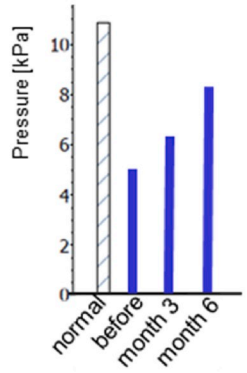

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	Before		Month 3		Month 6	
	Absolute	% of predicted	Absolute	% of predicted	Absolute	% of predicted
RV (L)	0.91	50	0,95	53	1,29	71
FVC (L)	2.26	76	2,13	72	2,44	83
TLC (L)	3.17	59	3,08	58	3,73	70
FeV1 (L)	1.8	67	1,92	71	2,07	77
FeV1/VC_{max} (%)	80	106	90%	121	85%	114
Peak flow (l/s)	3.91	66	4,68	79	5,89	100
DLCOc SB (mmol/min/kPa)	3.03	38	4.35	56	4.45	57
TLCOc /VA (mmol/min/kPa/l)	0.95	59	1.33	83	1.3	81

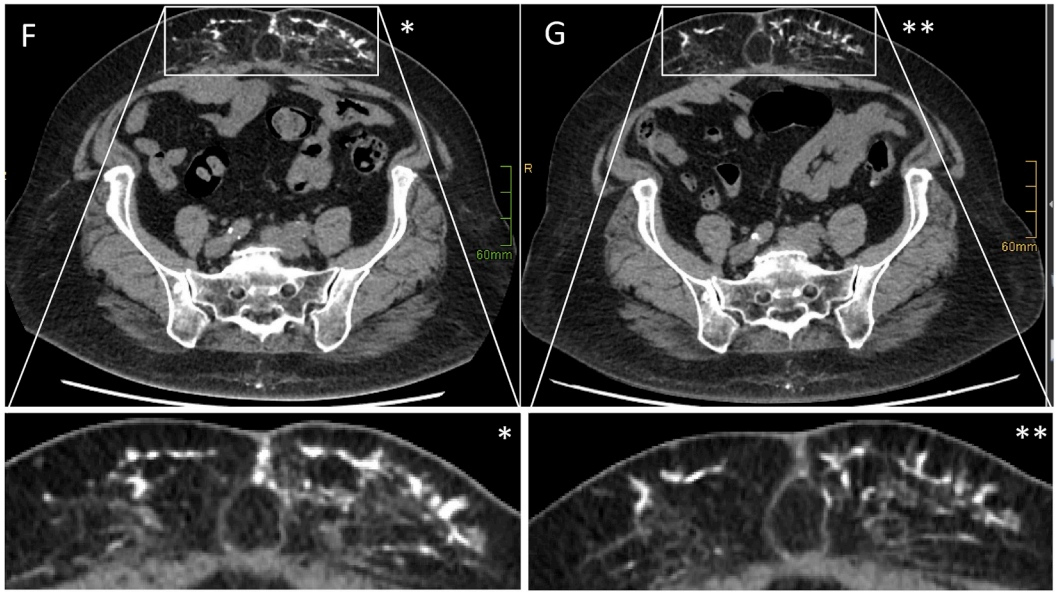

Fig. 2. (A) CT scan of the lungs of patient B at the diagnosis of AFOP showing progressive peribronchovascular and subpleural consolidations and bronchiectasis. (B) Temporary improvement with regressive subpleural and peribronchovascular infiltrates after rituximab treatment. (C) Regressive infiltrates with minor remaining consolidations ten weeks after start of tofacitinib. Pulmonary function and respiratory muscle strength testing were performed before and three and six months after start of tofacitinib (D, E). Repeated lung function measurements during the treatment phase demonstrated an increase in inspiratory muscle strength (D) and gain of lung volume and diffusion capacity (E). Abdominal CT scans before (G) and after 10 weeks of tofacitinib treatment (H) show decreasing soft tissue calcifications in the periumbilical region (asterisks).

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2019.03.003.

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