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Keywords: myocarditis; psoriasis; dilated cardiomyopathy; IL-17A



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Article

Interleukin 17A-Correlated Myocarditis in Patients with Psoriasis: Cardiac Recovery Following Secukinumab Administration

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Abstract: Background: Psoriasis (PS) is a common immune-mediated disease of the skin with possible extension to joints, aorta and eye. Myocardial inflammation has been rarely suggested. **Aims:** Report of PS-related myocarditis. **Methods and Results:** One hundred consecutive patients with PS were screened for cardiac involvement. Among them, five male patients (aged 56 ± 9.5 years) with moderate-severe form showed a dilated cardiomyopathy (LVEF <35%) with normal coronary arteries and valves. They underwent a left ventricular endomyocardial biopsy for evaluation of myocardial substrate. Endomyocardial samples were processed for histology and immunohistochemistry, including myocardial expression of Toll-Like Receptor 4 (TLR4) and interleukin-17A (IL-17A), which plays a major role in psoriasis pathogenesis; real-time PCR for cardiotropic viruses and Western blot analysis for myocardial expression of IL-17A. Patients' sera were tested for anti-heart autoantibodies. An active lymphocytic myocarditis was revealed in all 5 patients, characterized by absence of viral genomes at PCR, positive anti-heart autoantibodies, overexpression of TLR-4 and enhancement of IL-17-A at western blot analysis showing a 2,48-fold increase in psoriatic myocarditis compared with no psoriatic myocarditis and a 6-fold increase compared to myocardial controls. Treatment included combination of prednisone (1 mg/Kg daily for 4 weeks, tapered to 0.33 mg/Kg) + azathioprine (2 mg/Kg, daily) in 3 pts or secukinumab (SK, 100 mg/monthly) in 2 pts for 6 months. LVEDD and LVEF improved in the first 3 pts (-14% and + 118%, respectively) while completely recovered (LVEF > 50%) in the last 2 pts on SK. **Conclusion.** IL-17A-related myocarditis can occur in up-to 5% of patients with psoriasis. It manifests as a progressive dilated cardiomyopathy. It may completely recover following SK administration.

Keywords: myocarditis; psoriasis; dilated cardiomyopathy; IL-17A

1. Introduction

Psoriasis (PS) is a common immune-mediated disease which affects 1–3% of the population (1). The pathogenesis of PS is unknown. It is probably correlated to a complex interaction between environmental factors, genetic predisposition and characteristics of the immune system. Myocardial involvement in psoriasis is poorly investigated. Single case reports and small observational studies suggest a possible relationship between Psoriasis and cardiomyopathy (2-8). Eliakim-Raz et al (2) reported the presence of cardiomyopathy in 20 patients (0.87%) among 2292 hospitalized patients with psoriasis, 10 (0.43%) of which having a dilated cardiomyopathy. However, the pathogenesis of this correlation is still unclear. IL17-A is the major cytokine implicated in psoriasis pathogenesis and it is overexpressed in psoriatic skin (1, 9). Secukinumab, a IL17-A neutralizing IL17 antibody has been demonstrated to have a remarkable clinical efficacy in patients with moderate-to-severe psoriasis (10-11).

Aim of the present study is to determine the incidence and pathogenesis of myocardial inflammation in patients with Psoriasis as well as its most appropriate treatment.

2. Materials and Methods

Patient population

One hundred consecutive patients (62M/38F, mean age 55 ± 13.7 years) with a diagnosis of Psoriasis of various severity were screened for possible cardiac involvement. Severity of the disease was defined on the basis of PASI (Psoriasis Area Severity Index) (12,13) and on the presence of comorbidity. In particular 28% of patients showed mild skin involvement, while 56% had a moderate and 16% a severe form of the disease; 23 patients had also arthritis and 4 patients ocular disease. Among them, five male patients, (mean age 56 ± 9.5 years) with moderate/severe psoriasis presented cardiac dilatation with remarkable reduction of ejection fraction, normal valves and absence of additional clinical problems. To investigate the cause of cardiac compromise those patients underwent non-invasive cardiac investigations including echocardiography and cardiac magnetic resonance (CMR) and an invasive cardiac study including coronary angiography and left ventricular endomyocardial biopsy.

Clinical studies

Clinical assessment, resting electrocardiogram, Holter monitoring, 2D-echocardiography and cardiac magnetic resonance (CMR) were performed at baseline in all patients. Cardiac catheterization, angiography, and left or biventricular endomyocardial biopsy were also performed, after patients had given informed consent. The New York Heart Association (NYHA) classification was used to assess functional capacity determined by means of a questionnaire. The study complies with the Declaration of Helsinki, the locally appointed ethics committee (opinion number 2016-003014-28 (FARM12JCN)) approved the research protocol, and informed consent was obtained from all subjects.

Cardiac Magnetic Resonance (CMR)

CMR exams were performed on a 1.5 T scanner (Magnetom Avanto; Siemens Medical Systems, Erlangen, Germany) using body and phase-array coils. The CMR protocol included the following elements: (i) cine balanced steady-state free precession (cine-bSSFP) images were acquired during breath holds in the short-axis (from the base to the apex, 10–12 slices), 2-chamber, and 4-chamber planes (TR: 51.3 ms, TE: 1.21 ms, flip angle: 45° , slice thickness: 8 mm, matrix: 256×256 , field of view: 340–400 mm, voxel size: $2.0 \times 1.3 \times 8.0$ mm); (ii) black blood T2-weighted breath-hold short tau inversion recovery (T2w STIR) images were obtained using a segmented turbo spin echo triple inversion recovery technique on short axis (from the base to the cardiac apex, 8–10 slices), 2 chambers and 4 chambers planes (TR: 2 R–R intervals, TE: 75 ms, flip angle 180° , TI: 170 ms, slice thickness: 8 mm, field of view: 340–400 mm, matrix: 256×256 , voxel size: $2.3 \times 1.3 \times 8$ mm); (iii) ECG-gated single-shot Modified Look-Locker inversion recovery sequence with a 5(3)3 scheme and motion-correction postprocessing algorithm (Siemens WIP package no. 448) for native T1 mapping was acquired on short-axis basal, mid ventricular and apical planes (TR: 314 ms; TE: 1.12 ms; flip angle: 35° ; TI: 200 ms; slice thickness: 8 mm; field of view: 340–400 mm; matrix: 256×256 ; voxel size: $2.1 \times 1.4 \times 8$ mm); (iv) T2 mapping was acquired with a T2-3pt GRE in short axis through basal, mid ventricular and apical planes (TR: 239 ms; TE: 1.13 ms; flip angle: 12° ; slice thickness: 8 mm; field of view 340–400 mm; matrix 256×256 ; voxel size: $2.5 \times 1.9 \times 8$ mm); (v) late gadolinium-enhanced (LGE) imaging was performed 15 minutes after bolus injection of 0.1 mmol/kg of body weight of gadobutrol (Gadovist, Bayer AG, Leverkusen, Germany) at a flow rate of 2.0 ml/s, using a phase sensitive inversion recovery gradient echo (PSIRGRE) sequence (TI: 250–300 ms, TR: 9.6 ms; TE: 4.4 ms; matrix: 256×208 ; flip angle 25° ; slice thickness 8.0 mm; slice spacing 2.0 mm).

Endomyocardial biopsy studies

Endomyocardial biopsies (5-8 fragments/each patient) were performed in the septal–apical region of the left ventricle. Samples were either fixed in formalin and paraffin-embedded for histology and immunohistochemistry or snap frozen for molecular biology and western blot analysis.

Histology and immunohistochemistry

For histological analysis, the endomyocardial samples were fixed in 10% buffered formalin and paraffin embedded. Five-micron-thick sections were stained with haematoxylin and eosin and Masson trichrome.

For the phenotypic characterization of the inflammatory infiltrates, immunohistochemistry for Cluster of Differentiation (CD)3, CD20, CD43, CD45RO, and CD68 was performed (all Dako, Carpinteria, CA, USA). The presence of an inflammatory infiltrate ≥ 14 leucocytes/mm² including up to 4 monocytes/mm², with the presence of CD3-positive T-lymphocytes ≥ 7 cells/mm² associated with evidence of degeneration and/or necrosis of the adjacent cardiomyocytes, was considered diagnostic for myocarditis. The number of CD3-positive cells was manually counted using a tally counter on high power field ($\times 400$) scanning the entire slide. The area of tissue samples was measured by means of a computerized system (Imaging Software/NIS-Elements AR 4.30, Nikon Instruments Inc., Melville, NY, USA). The number of CD3-positive cells was expressed as number of cells per square millimetre. Morphometric evaluation was performed by a pathologist blinded to clinical data.

For the assessment of TLR4, and IL-17A expression myocardial sections were incubated with a mouse monoclonal TLR4 antibody 1:10 dilution (HTA125, Santa Cruz Biotechnology Inc., Dallas, TX, USA), (rabbit polyclonal IL 17/A antibody 1: 250 dilution, Abcam Cambridge Biomedical Campus, UK) and a peroxidase/anti-peroxidase complex, followed by labelling with the chromogen diaminobenzidine (Dako). A semiquantitative evaluation of the cytoplasmic immunoreactivity for TLR4 and IL-17A (grading from 0 to 4) was applied. For TLR4 and IL-17A grade 0 was attributed to absence of immunostaining, grade 1 to 1–10% positive cardiomyocytes, grade 2 to 11–30%, grade 3 to 31–60% and grade 4 to $>60\%$ positivity. Appropriate positive and negative controls were used, and tissues incubated with antibody diluent, without the primary antibody, followed by incubation with secondary antibodies and detection reagents (negative control). In addition, samples were incubated with antibody diluent, supplemented with a non-immune immunoglobulin of the same isotype (IgG2a) and concentration as the primary monoclonal antibody. The samples were then incubated with the secondary antibody and detection reagents. These steps were adopted to rule out that what appears to be specific staining was not caused by non-specific interactions of immunoglobulin molecules with the samples.

Molecular biology studies

In all patients at baseline a PCR for the most common cardiotropic viruses (adenovirus, enterovirus, influenza A and B viruses, Epstein–Barr virus, Parvovirus B19, Hepatitis C virus, Cytomegalovirus, Human Herpes Virus 6, Herpes Simplex virus A and B) was performed to exclude a myocardial viral infection.

Western Blot Analysis

We determined the expression of IL-17A in frozen myocardial tissue. Results were compared with values from surgical control unloaded myocardium (papillary muscle of patients with mitral stenosis undergoing valve replacement).

Protein Isolation and Western Blot

Heart tissue samples were treated as previously described. The expression of Interleukin 17A, molecular weight 18 kDa, was visualized by using Anti IL-17A antibody polyclonal (1:1000, Abcam Cambridge Biomedical Campus, UK). Anti- α -sarcomeric actin antibody (1:500, Sigma-Aldrich), molecular weight 43 kDa, was used for normalization. Signal was visualized using a secondary horseradish-peroxidase-labeled goat anti-rabbit antibody (goat anti-rabbit IgG-HRP 1:5000, Santa Cruz Biotechnology) and enhanced chemiluminescence (ECL Clarity Bio-Rad). The purity as well as equal loading (40 γ) of the protein was determined by Nanodrop One (ThermoFisher). To normalize target protein expression, the band intensity of each sample is determined by densitometry with Image J software. Next, the intensity of the target protein is divided by the intensity of the loading control protein. This calculation adjusts the expression of the protein of interest to a common scale and reduces the impact of sample-to-sample variation. Relative target protein expression can then be compared across all lanes to assess changes in target protein expression across samples. Digital images of the resulting bands were quantified by the

Image Lab soft-ware package (Bio-Rad Laboratories, Munchen, Germany) and expressed as arbitrary densitometric units.

Statistical analysis

Statistical analysis was performed by the GraphPad Prism package, version 5.02 (Graphpad Software Inc., San Diego, CA). Comparison between groups was performed with Mann Whitney non parametric test was used. A p value less than 0.05 was considered statistically significant.

3. Results

Cardiac studies

Among our psoriatic population, five male patients (mean age 56 ± 9.5 years) showed a dilated cardiomyopathy (LVEF $<35\%$) with normal coronary arteries and valves. Their baseline clinical and instrumental data are reported in Table 1.

All five patients presented moderate/severe skin involvement. Two patients had also arthritis and one patient eye disease (dry eye). Baseline NYHA Class was III/IV. Electrocardiogram documented premature ventricular contractions, supraventricular tachycardia and non-sustained ventricular tachycardia in 3 patients, atrial fibrillation in 1 patient and ST segment/T wave abnormalities in 1 patient (Figure 1 panel A). At 2d-echo all patients exhibited left ventricular dilation (left ventricular end-diastolic diameter, LVEDD = 64.6 ± 8.01 mm) with severe reduction of ejection fraction (LVEF = $20.2 \pm 5.6\%$) and high filling pressure ($E/E' > 12$ mmHg); moreover, right ventricular dysfunction (tricuspid annular plane systolic excursion, TAPSE < 15 mm) was present in 3 patients and pericardial effusion in 2 patients. STIR T2 weighted CMR images demonstrated hyperintensity as well as native T1 and T2 maps showed a diffuse increase of myocardial T1 and T2 values (Figure 1 panels B, C) due to diffuse edema. CMR (Figure 1 panels D, E and video) confirmed the hypokinetic dilated cardiomyopathy. Late gadolinium enhanced images did not show any fibrotic area (Figure 1 panels F, G) except in 2 patients.

All these 5 patients underwent a left ventricular endomyocardial biopsy for evaluation of myocardial substrate. At cardiac catheterization elevated filling pressures were documented (left ventricular end diastolic pressure, LVEDP > 12 mmHg) with normal coronary network at angiography. Endomyocardial biopsy was a safe procedure with no side effects in any patient.

Histology and Immunohistochemistry

All 5 pts exhibited a virus negative lymphocytic myocarditis with over expression of TLR4, IL17A and positive anti-heart autoantibodies cross-reactive with skeletal muscle (Figure 2 and Figure 3 panels A-D) (14).

Semiquantitative evaluation of immunostaining (grades from 0 to 4) for IL-17A and TLR4 showed an increased cardiomyocyte expression of IL-17A in psoriasis myocarditis compared with no psoriatic patients and vs controls (respectively $3,95 \pm 0,13$ vs $1.91 \pm 0,5$ and $3,95 \pm 0,13$ vs $0,19 \pm 0,2$) (Figure 3 panel E)

Immunostaining for TLR4 showed an overexpression of TLR4 in PS patients vs no psoriasis myocarditis and vs controls. (3.44 ± 0.51 vs 1.56 ± 0.2 and 3.44 ± 0.51 vs $\pm 0.18 \pm 0.17$).

Western Blot

Protein analysis showed a 2,48-fold increase in IL-17 A protein expression in psoriasis myocarditis compared with no psoriasis myocarditis and a 6-fold increase when compared with controls (respectively 51560 ± 899 vs $20734,5 \pm 2502$, $p = 0.037$, $p < 0.01$ and 51560 ± 899 vs 8600 ± 1055 , $p = 0.005$, $p < 0.001$).

Treatment

All 5 patients showed virus-negative virus negative lymphocytic myocarditis, 3 of them were treated for 6 months with immunosuppressive therapy including 1 mg/kg prednisone daily for 4 weeks followed by 0.33 mg/kg daily for additional 5 months and 2 mg/kg azathioprine daily for 6 months according to TIMIC protocol (15) and 2 patients with IL-17A inhibitor (100 mg monthly for 6 months). All patients also received appropriated therapy for heart failure with beta-blockers,

angiotensin receptor-neprilysin inhibitors/ACE inhibitors/angiotensin receptor blockers, mineralocorticoid receptor antagonists and diuretics according to current ESC Guidelines (16).

Follow-up

At 6-month-follow-up (Table 2), 3 patients treated with prednisone and azathioprine improved with NYHA Class reduction from III to II and LVEF increased from 22.6% to 48.6% while 2 patients on SK recovered completely with reduction of NYHA Class from III/IV to I, LVEED decreasing from 66 to 53 mm and normalization of LVEF from 16% to 55% (Figure 1 panels H, I and video 1). Arrhythmias and ST segment/T wave abnormalities (Figure 1 panel J) on electrocardiogram disappeared. CMR showed resolution of edema on STIR T2 weighted image and reduction of native T1 and T2 values on mapping sequences. Patients 1 and 5 exhibited persistence of late gadolinium enhancement as a consequence of myocardial fibrosis. Skin lesions almost completely disappeared (Figure 2 panel B) while arthritis improved and dry eye healed.

3.2. Figures and Tables

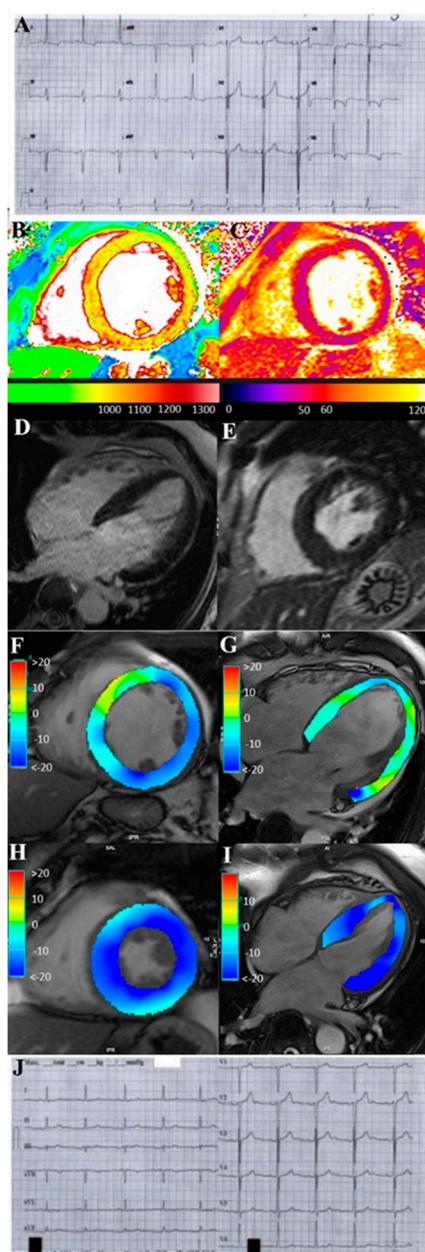


Figure 1. ECG (panel A and J) and CMR (panel B-I) findings of pt 5 with severe PS-related myocarditis at baseline and following 6 months SK administration.

ECG shows complete normalization of ST-T abnormalities after therapy (panel A: ecg before therapy, panel J ecg post therapy).

CMR: Native T1 (B) and T2 (C) maps show a diffuse increase of myocardial T1 and T2 values due to diffuse edema during acute phase (B-C). CineMR images, acquired on mid ventricular short axis (D) and four chamber (E) views at end systolic phase show a marked reduction in LV function, respectively visualized as impairment of GLS and GCS strain values. Late gadolinium enhanced images (F-G) do not show any fibrotic or necrotic myocardial areas. CineMR images at follow-up (H-I) show a complete recovery of LV function with normal GCS and GLS strain values. LV: left ventricle; GCS: Global Circumferential Strain; GLS: Global Longitudinal Strain.

Video 1: CineMR dynamic images acquired at baseline and at follow-up.

CineMR dynamic images of Patient 5 acquired at baseline during subacute phase of psoriasis-related myocardial injury (upper row) and at 18 months follow-up (lower row), after IL-17A monoclonal antibody therapy. Images acquired on mid ventricular short-axis and four chamber views show a marked reduction of LV function and LV dilation at baseline (EF: 16%), with total recovery of contractile function at follow-up (EF: 55%).

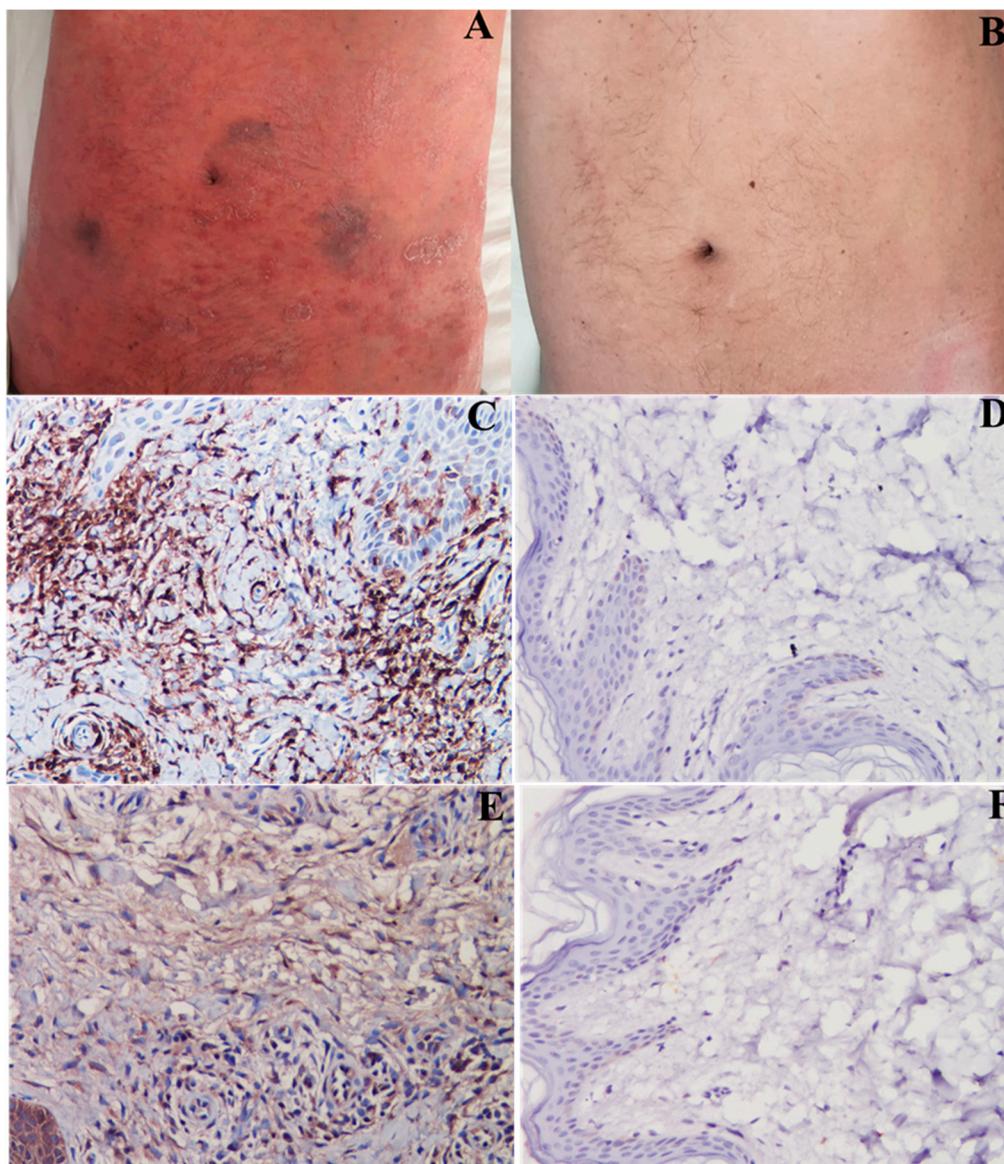


Figure 2. Severe psoriatic skin lesions from pt 5 that completely recover after SK administration. Panels A-B: skin dermatitis (A) and (B) its recovery. Panels C-F: Complete recovery from skin inflammation. (C: extensive T-lymphocytic (CD45Ro+) inflammatory infiltrates); E: Overexpression of IL 17-A that disappears (panels D and F respectively) after treatment.

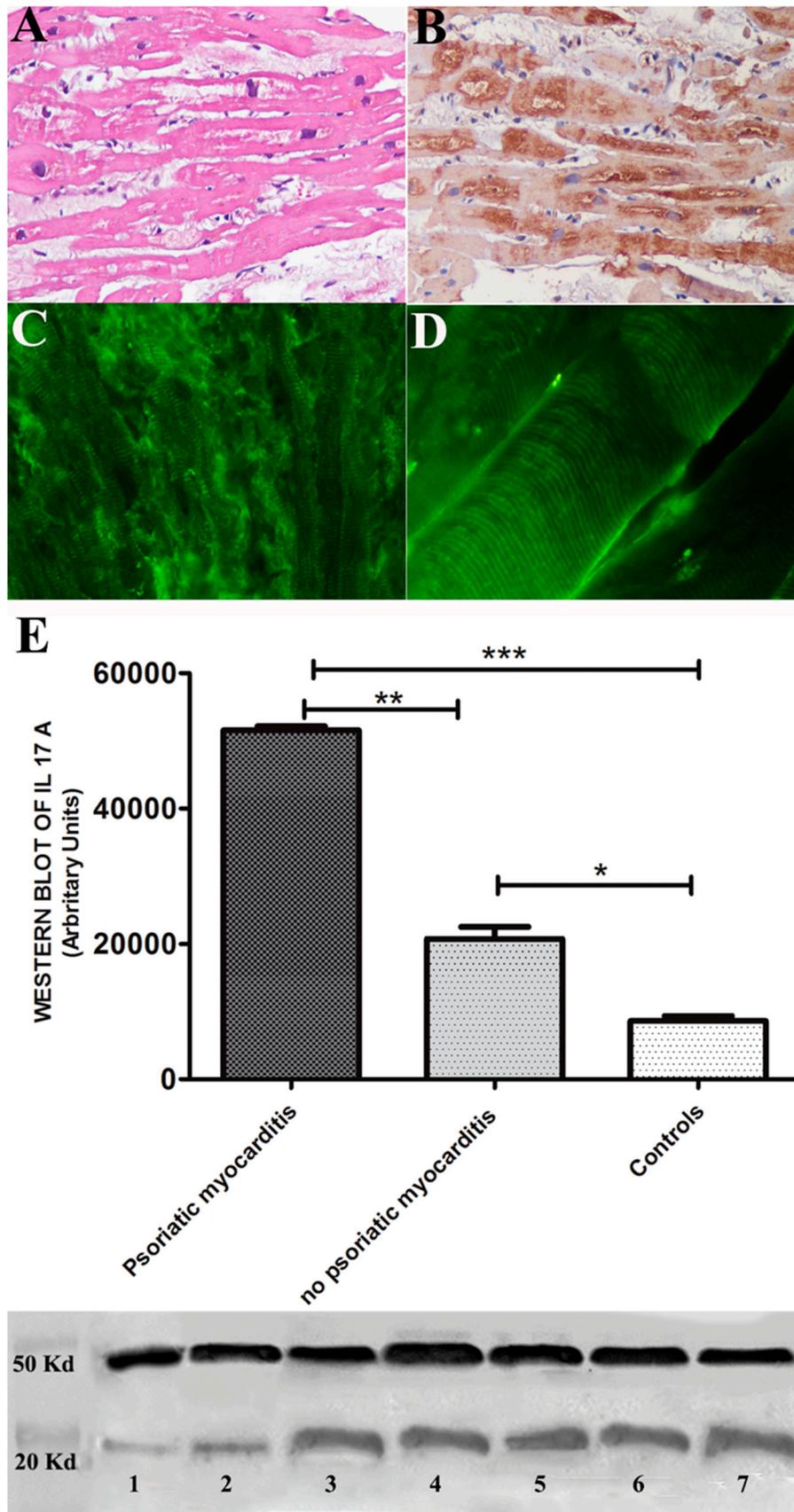


Figure 3. Endomyocardial biopsy findings from pt 5 with PS-related myocarditis including histology (panel A). Immune-histochemistry for IL 17-A (panel B) and anti-heart abs (panels C, D). It shows an active lymphocytic myocarditis with overexpression of IL 17-A and positive anti-heart abs (panel C), cross-reacting with skeletal muscle (panel D).

Graphs document western blot of IL -17 A (18 Kda) and showed a 2,48-fold increase in IL-17 A protein expression in psoriatic myocarditis compared with no psoriatic myocarditis and a 6-fold increase when compared with controls (respectively 51560 ± 899 vs $20734,5 \pm 2502$, $p= 0.037$, $p<0.01$ and 51560 ± 899 vs 8600 ± 1055 , $p=0.005$, $p< 0.001$). Alpha sarcomeric actin (43 kDa) was used as a loading control (panel E)

Marker; lane 1= normal control, lane 2= no psoriatic myocarditis, lane 3= pt 1, lane 4= pt 2, lane 5= pt 3, lane 6= pt 4, lane 7= pt 5.

Table 1. Baseline clinical and instrumental data of the five patients with psoriasis related myocarditis.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age / sex	67/M	52/M	54/M	65/M	44/M
Severity of skin psoriasis	Moderate	Severe	Moderate	Moderate	Severe
Presence of Arthritis	No	No	Yes	No	Yes
Eye involvement	No	No	No	Yes (dry eye)	Yes (dry eye)
NYHA Class	III	III	III	III	IV
ECG	PVC *	AF †	SVT‡ and NSVT§	NSVT §	ST-T abn
2d-Echocardiogram					
LVEDD ¶ (mm)	72	67	55	68	65
LVEF ** (%)	18	20	30	17	16
Left atrium (volume, ml)	60	68	50	70	126
E/E' †† ratio	30	28	22	25	29
TAPSE (mm) ††	14	13	24	18	16
Pericardial effusion	No	No	No	Yes	Yes
Cardiac Magnetic Resonance					

<i>LVEDV</i> *** (ml/m ²)	108.7	131.0	130.1	114.08	217.5
<i>LVESV</i> ++ (ml/m ²)	91.5	110.6	108.2	95.6	181.0
<i>LVEF</i> %	15.8	20.3	32.7	16.1	16.7
<i>MWT</i> ††	13	11	10	11	13
<i>LV mass</i> §§ (g/m ²)	79	85.6	97.1	80.2	158.1
<i>Edema</i>	No	No	No	Yes	Yes
<i>LGE</i>	Yes	No	No	Yes	Yes
<i>T1 global</i> ± SD ¶¶ (ms)	1285±131	1015±153	1020±81	1056±96	1071±52
<i>T2 global</i> ± SD ¶¶ (ms)	56±14	52±9	51±6	50±8	50±6
Coronary arteries	Normal	Normal	Normal	Normal	Normal

* premature ventricular contractions; † atrial fibrillation; ‡ supraventricular tachycardia; § non-sustained ventricular tachycardia; || ST segment/T wave abnormalities; ¶ left ventricular and-diastolic diameter; ** left-ventricular ejection fraction; †† ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E'); ‡‡ tricuspid annular plane systolic excursion; *** left ventricular end-diastolic volume; †† left ventricular end-systolic volume; §§ left ventricular mass; ||| late gadolinium enhancement; ¶¶ standard deviation.

Table 2. Six-month-follow-up clinical and instrumental data of the five patients with psoriasis related myocarditis.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age / sex	67/M	52/M	54/M	65/M	44/M
Therapy	Az *+ Pr†	Az *+ Pr†	Az *+ Pr†	SK‡	SK‡
Severity of skin psoriasis	Mild	Mild	Mild	Healed	Healed
Presence of Arthritis	No	No	Yes (improved)	No	Yes (improved)
Eye involvement	No	No	No	No	No

NYHA Class	II	II	II	I	I
ECG	normal	Sinus rhythm	SVT§, PVC	normal	normal ¶
2d-Echocardiogram					
LVEDD** (mm)	59	56	50	55	51
LVEF++ (%)	47	49	50	55	55
Left atrium (volume, ml)	62	45	53	40	50
E/E' ratio ††	13	11	12	10	8
TAPSE*** (mm)	19	20	23	25	24
Pericardial effusion	No	No	No	No	No
Cardiac Magnetic Resonance					
LVEDV++ (ml/m ²)	98.7	83.0	72.5	99.9	82.7
LVESV †† (ml/m ²)	52.6	42.0	34.4	45.2	37.9
LVEF %	46.7	49.2	50.5	54.3	55.2
MWT §§	14	11	9	11	13
LV mass (g/m ²)	75	68.5	63	69.3	88.5
Edema	No	No	No	No	No
LGE ¶¶	Yes	No	No	Yes	Yes
T1 global ± SD**** (ms)	1010±117	970±101	982±106	980±102	1030±62
T2 global ± SD**** (ms)	41±5	46±6	49±9	42±5	46±7

* Azathioprine; † Prednisone; ‡ Secukinumab; § supraventricular tachycardia; || premature ventricular contractions; ¶ ST segment/T wave abnormalities; ** left ventricular and-diastolic diameter; ††left-ventricular ejection fraction; †† ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E'); *** tricuspid annular plane systolic excursion; ††left ventricular end-diastolic volume; †† left ventricular end-systolic volume; §§ maximal wall thickness; |||| left ventricular mass; ¶¶ late gadolinium enhancement; **** standard deviation.

4. Discussion

Psoriasis (PS) is an immune-mediated inflammatory disease with prevalent skin involvement. Indeed, a systemic spreading of the disease has been recognized with possible extension to joints (17), aorta (18) and eye (19). Myocardial inflammation has been previously suggested in the setting of dilated cardiomyopathy manifesting in subjects with PS but histologic confirmation as well as pathogenetic correlations with the former disease have not been provided so far.

This is the first study that analyzes the incidence of cardiomyopathy in the context of a large population affected by PS, its histologic and molecular substrate obtained by means of endomyocardial biopsy and finally its most appropriate treatment.

In the present report, a cardiomyopathy has been recognized in 5 of 100 consecutive patients with PS. These 5 male patients had a moderate to severe form of the disease with involvement of skin and other districts as joints in two and eye in one. Histology of endomyocardial samples documented a virus-negative lymphocytic myocarditis with overexpression of IL17-A. These findings were similar to those observed in the corresponding skin biopsy (Figure 2 Panel A) and suggest myocardial inflammation be an extension of PS to the heart. Overexpression of IL17-A was ascertained by both immunohistochemistry and western blot analysis which showed 2.5-fold increase the value obtained in no-psoriatic myocarditis and 6-fold increase the normal myocardial control. Immuno-pathogenesis of myocardial inflammation has been also supported by myocardial positivity of TLR4 at immunohistochemistry as well as presence in the patients' sera of anti-heart abs which cross-reacted with skeletal muscle (Figure 3 panel D). This last finding suggest that symptoms connected with skeletal muscle damage as pain, cramps, and functional impairment may accompany the manifestations of severe forms of PS.

As far as treatment of PS-related inflammatory cardiomyopathy is concerned, although limited to few cases, two alternatives have been tested including TIMIC protocol (15) (combination of prednisone and azathioprine) commonly adopted for virus-negative inflammatory cardiomyopathy and Secukinumab, specific inhibitor of IL17-A (10,11) which has obtained the control of skin lesions in the advanced PS. In this report, although both approaches have given positive results, administration of Secukinumab for 6 months has been followed by resolution of skin lesions (Figure 2 panel B) and normalization of cardiac parameters with LVEF rising from 16 up to 55 %. No side effects were reported from the two type of treatment.

Practical Implications

Immune-mediated myocardial inflammation can be part of systemic manifestations that applies to the advanced forms of PS. While its suspect can arise following application of cardiac magnetic resonance, its definite recognition requires an endomyocardial biopsy showing a virus-negative inflammatory cardiomyopathy characterized by overexpression of IL17-A. Although immunosuppression is clinically beneficial, treatment with Secukinumab appears as the most effective therapeutic solution with complete recovery of skin and cardiac damage.

5. Conclusions

IL-17A-related myocarditis can occur in up-to 5% of patients with psoriasis. It manifests as a progressive dilated cardiomyopathy. It may completely recover following SK administration.

Author Contributions: AF designed the study, participated in and lead the categorization of the subjects, and wrote the manuscript, NG,LD , performed the CMR and collected the data, RV, RS, categorized and organized the data and experiment. AF, and AGR discussed and verified the cases. All authors participated in drafting the manuscript and approved the final manuscript

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Institutional Review Board Statement: This study was approved by the ethics committee, opinion number 2016-003014-28 (FARM12JCXN).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

Acknowledgments: All authors.

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