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Systemic Amyloidosis Secondary to Psoriasis: A Rare, Autoimmune and Genetically-Determined Disorder That Is Amenable to Treatment with Cyclosporin A

—Cyclosporin A for Psoriasis-Induced Amyloidosis

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Abstract

Background: Systemic secondary amyloidosis (SSA) is associated with chronic inflammatory disorders and/or chronic infections. **Patients and Methods:** Over the past 10 years; a total of 21 patients, with long-term (≥17 months) and extensive psoriasis (P) with psoriasis area severity index (PASI) >29, were evaluated. **Results:** Two patients had nephrotic syndrome (proteinuria 3.9 and 3.6 g/day) and decrease creatinine clearance (46 and 62 ml/minute). Their renal biopsy revealed Congo-red (+) nodular glomerulosclerosis that lacked immune-deposits and resisted wash with K-permanganate wash indicating SSA. Three months subsequent to Cyclosporin A (CyA) therapy with 100 mg twice daily; psoriasis improved in all patients with decrease in (PASI) from ≥29.5 to ≤3.5 + 1. In the 2 patients with SSA; proteinuria decreased to 2.1 and 1.8 g/day and creatinine clearance improved to 51 and 69 ml/minute. Such improvement persisted up to ≥2 years of follow up and up to ≥78 months in patients with SSA. **Conclusion:** psoriasis-induced SSA is an autoimmune disease, with genetic predisposition that is amenable to CyA therapy.

Keywords

Amyloidosis, Psoriasis, Nephrotic Syndrome, Cyclosporin A

1. Introduction

Systemic amyloidosis is a disease characterized by the extracellular deposition of

insoluble misfolded beta-sheet fibrillar proteins [1]. According to etiology, 4 types of systemic amyloidosis are most frequently seen: 1) amyloid light-chain (AL) due to clonal plasma cell dyscrasia, 2) amyloid amyloidosis (AA) due to elevated serum amyloid A protein associated with inflammation *i.e.* secondary systemic amyloid (SSA), 3) amyloidosis due to mutations of the precursor protein transthyretin leading to hereditary and familial forms, and 4) amyloidosis beta-2 microglobulins amyloidosis (in severe renal failure and dialysis patients) [2]. Systemic amyloidosis is a rare disease with an estimated prevalence of 0.8/100,000 population; of whom 3/4 are secondary forms [3]. SSA is an immune-mediated disease induced by chronic inflammatory disorders and/or chronic infections. These conditions lead to cytokine expression that results in the overproduction of amyloid A protein by the liver [4]. Systemic deposition of such insoluble fibrillar proteins can lead to life-threatening organ failure viz. heart, kidneys, and nervous system [5]. Forty-eight disorders were found to be strongly associated with SSA viz. bacterial infections, chronic rheumatological disorders, vasculitis, inflammatory bowel diseases, familial Mediterranean fever, and hematological and solid organ tumors. However, the most common causes are poorly treated tuberculosis and refractory rheumatoid arthritis [6]. Worldwide; only a few and treatment-refractory cases were reported in association with psoriasis (P) [7] [8]. Since prognosis depends on early diagnosis and effective treatment; we report our experience with P-induced SSA and its beneficial response to CyA.

2. Patients and Methods

During the period 1st of January 2014 to 31st December 2023, 21 adult patients with refractory severe P were selected for treatment with CyA. P severity was assessed by Psoriasis Area and Severity Index (PASI). It was calculated as follows: 1) The severity of intensity, of redness, thickness, and scaling, was expressed as 0 - 4. 2) The three intensity scores are added up for each of the four body regions (head & neck, upper limbs. Trunk and lower limbs). Each subtotal was multiplied by the body surface area, and 3) summation of score [9]. For the study; patients were included if they had: 1) age > 14 years; 2) P diagnosed clinically and confirmed by histopathological examination; 3) Severe and extensive disease with psoriasis area and severity index (PASI) ≥ 10 [9]; 4) Persistent or relapsing disease despite treatment with Corticosteroids, retinoids, Methotrexate and narrow-band ultraviolet light exposure (UVB); 5) No evidence of recent or recurrent exposure to solar or traumatic injuries, primary skin infections, HIV, drugs viz. lithium, beta blockers, antimalarial, antibiotics (penicillin and sulphonamides), psychotropic agents (nitrazepam and trazodone), amiodarone, Mestranol, Morphine, NSAIDS and sudden withdrawal of corticosteroids. Initially, all patients were treated, as burn cases, with intravenous fluids with/without human albumin to control shock-state and replace the deficient electrolytes. They also had received broad-spectrum antibiotics to protect against skin and chest infec-

tions as well as topical treatments. Cy A was given, on day 1, orally, as syrup or neural capsules, in an initial dose of 3 mg/kg/day in 2 divided doses. Subsequently, the dose was further adjusted every 2 weeks to achieve a trough level within therapeutic range (82 - 160 ng/ml; TDx Cyclosporin, monoclonal assay). By the 3rd months and after achieving adequate response; the dose of Cy A was reduced gradually to the minimal dose that prevents relapse. After their initial in-hospital stabilization, patients were assessed every 2 weeks for 6 weeks, every month for 3 months then every 2 months. They were assessed clinically using PASI scores and with laboratory tests that included complete blood count as well as renal and liver function tests. Creatinine clearance (CrCl) and daily protein excretion (PE) were done at times; 0, 3 months, 2 years and at the end of follow up. After 3 months of therapy; the dose of Cy A was reduced gradually, by 25 mg/day every 2 month, till reaching the minimal maintenance dose.

Statistical analysis:

SPSS statistical package version 26 was used for data entry and processing. The p-value ≤0.05 was used as the cut-off level for significance. Since age, duration of psoriasis, PASI, CrCl and PE were normally distributed; they were expressed as Means while duration of follow up was not normally distributed and hence it was expressed as Median (IQR). Comparison of age and duration of P between in both groups was done using T-test. On the other hand; comparison of the individual changes in PASI, CrCl and UP at different times (0, 3 months, 2 years) was done using T-test and the overall changes with ANOVA for repeated measures.

3. Results

During the study period, 2 of the 21 patients had shown significant renal disease (nephrotic range proteinuria and decreased CrCl that indicated kidney biopsy. The latter showed features typical of amyloidosis (**Figure 1**). The demographical data on the patients and their response to Cy A, after 3 months, 2 years and end of follow up, are summarized in **Table 1**. All patients were white adults and with equal sex distribution. They had severe psoriasis (PASI > 10) for ≥17 ± 4 months prior to inclusion. In most patients, skin lesions had healed rapidly within 3 months and PASI scores had dropped from 29 to 3.5 after 3 months, 2.4 after 2 years, and 2.3 by the end of follow up (>39 months). By the end of the study; all patients were controlled 50 mg twice daily except 2 who required 50 mg am and 25 mg pm. On follow up, there was no serious relapse, liver and kidney disease. Minor complications included; hirsutism and dark skin (n: 5) and gingival hyperplasia (n: 2). To avoid such side-effects, a trial to replace Cy A with Tacrolimus (Prograf) failed to maintain remission.

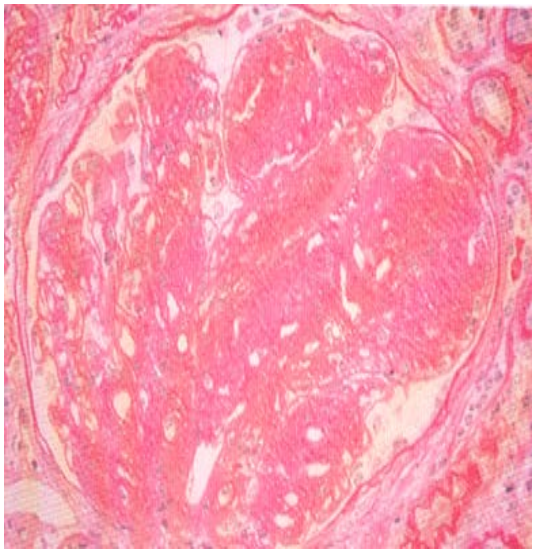
Response in patients with SSA:

As shown in **Table 1**, their proteinuria decreased to 2.1 and 1.8 g/day and creatinine clearance improved to 51 and 69 ml/minute by the 3rd month. Moreover; such improvement persisted till the end of follow up (104 & 78 months).

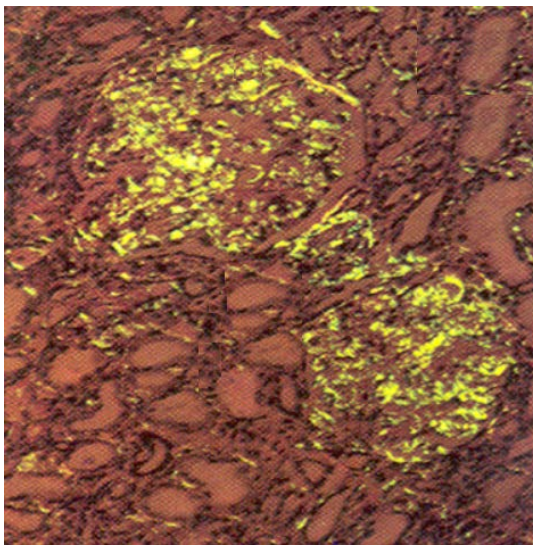
Table 1. Demographical data on psoriasis patients treated with Cyclosporin A.

Patients' characteristics	Patients with SAA* (n = 2)	Patients without SAA (n = 19)
Demographical data:		
Gender (F/M)	1/1	10/9
Age (years)	41 + 47	44 ± 8
Duration of psoriasis (months)	19 + 17	17 ± 4
Duration of follow up (months)	104 + 78	39 (50)
Response to Cyclosporin A treatment**:		
Time 0		
PASI	29 + 30	29 ± 5
CrCl	46 + 62	107 ± 15
PE	3900 + 3600	219 ± 46
Time 3 months		
PASI	2 + 3	3.5 ± 1
CrCl	51 + 69	102 + 16
PE	2100 + 1800	120 + 16
Time 2 years		
PASI	2 + 2	2.4 ± 1
CrCl	54 + 71	105 ± 14
PE	1200 + 1000	115 + 8
End of follow-up:		
PASI	3 + 1	2.3 + 2
CrCl	52 + 69	104 + 8
PE	1300 + 1000	121 + 11

*Data on the 2 patients are expressed individually; **Data on creatinine clearance (CrCl) are expressed in ml/minute and Protein excretion (PE) in mg/day; **Significant improvement (in both groups) from time 0 to 3 months, 2 years and end of follow up. N.B.: Expression of age, duration of psoriasis, PASI, CrCl and PE as Mean ± SD while duration of follow up as Median (IQR).



(a)



(b)

Figure 1. Photomicrograph of a kidney biopsy showing eosinophilic nodular mesangial sclerosis of amyloid deposits on H&E stain (a) and apple green on Congo red stain (b) at X200.

4. Discussion

AA is a major acute-phase reactant produced by hepatocytic transcriptional regulation via cytokines, especially interleukin (IL)-1, IL-6 and tumor necrosis factor under influence of a set of genes located on the short arm of chromosome 11 (AA1 genotype) [10]. After its secretion, AA rapidly associates with high-density lipoproteins, from which it displaces the pathogenic apolipoprotein A-I. Within 2 days of inflammation; AA level can rise from normal levels of 3 mg/l to over 1500 mg/l. Persistence of such high levels (>100 mg/L) were associated with systemic disease [4]. Persistence of such high-levels, in mal-treated patients, is associated with: 1) genetic (hereditary) sociability with amyloidogenic isoforms and

2) defect in clearance of AA by genetically defective macrophages (Polymorphisms of the mannose-binding lectin 2 (*MBL*-2) gene) and/or tissue metalloproteinases (defects in SAA1 genotype) [11] [12] [13]. Such genetic subtility to SSA in P was evident in our study. Despite their similar demographical characteristics, severity and long duration of P, only 2 out of 21 patients had developed significant and persistent renal disease (low creatinine clearance and heavy proteinuria and biopsy-proven glomerular amyloidosis). In our study, we proved that Cy A was able to cure P and it stabilized its subsequent SSA (progression of amyloid renal disease). At the molecular level; CyA acted by an early intervention at the level of hepatocyte transcriptional regulation [10]. Despite the rarity of SSA due to P; the latter is a common life-long autoimmune disease that affects 200 million patients worldwide of whom 20% with moderate to severe disease [14]. Improvement in P therapy and its associated complications can improve its morbidity, mortality, and even its quality of life. Despite the small number of our P patients; we did not encounter specific "psoriatic nephropathy" other than renal amyloidosis [15]. In our study, transient derangement in kidney function and mild proteinuria (>30 mg/24 h) were common in their severe initial presentation due to hypotension, hypovolemia, infection and previous-use of NSAIDs. Moreover, in P-patients with kidney disease, kidney biopsy is essential to exclude other etiologies viz. IgA disease before embracement on diagnosis of P-induced SAA [16].

5. Conclusion

P-induced SSA is an autoimmune disease, with genetic predisposition and fortunately amenable to CyA therapy.

Authors' Contributions

Concept development and organization as well as editing by prof/Kamel El-Reshaid. Data collection and processing by Dr. Shaima Al-Bader. Biopsies' processing and interpretation: Dr. John Patrick Madda. All authors have read the article and agreed with the final manuscript version.

Conflicts of Interest

1) Statement of ethics:

The case was reported according to World Medical Association Declaration of Helsinki.

There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

2) Conflict of interest statement:

The authors declare no conflicts of interest regarding the publication of this paper.

3) Funding Sources:

The authors did not have any funding sources for this article.

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