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Fatal Connective Tissue Disease with Antinuclear Antibodies Following PUVA Therapy

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Bruze M, Krook G, Ljunggren B. Fatal connective tissue disease with antinuclear antibodies following PUVA therapy. *Acta Derm Venereol (Stockh)* 1984; 64: 157–160.

Antinuclear antibodies with a nucleolar staining pattern appeared in a psoriasis patient during PUVA therapy. No antinuclear antibodies were found after the termination of PUVA but they reappeared one year later together with symptoms consistent with a connective tissue disease. The course was fatal and the clinical and the laboratory investigations suggested a scleroderma-like syndrome. *Key words: Nucleolar staining pattern; Ultraviolet irradiation.* (Received June 15, 1983.)

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Photochemotherapy with 8-methoxypsoralen and long wave ultraviolet light (PUVA) was introduced in 1974 for the treatment of psoriasis and has since then become a well established and effective form of therapy (1). Short term side effects are well known and usually harmless, while possible long-term risks still have to be evaluated. Screening for antinuclear antibodies (ANA) has been a routine in order to avoid exacerbations in patients with an undetected connective tissue disease, mainly systemic lupus erythematosus (SLE). As a consequence of this screening the generation of ANA during PUVA therapy was discovered (2, 3). Although no general pathological significance has been ascribed to these ANA so far, two psoriasis patients have been reported developing SLE (4) and a SLE-like syndrome (5) during PUVA therapy.

Recently we have studied a PUVA patient who developed ANA followed by a connective tissue disease.

CASE REPORT

A 61 year-old woman first consulted a dermatologist in 1976 with a history of a scaling eruption of her elbows, knees, palms and soles for one year. The clinical diagnosis was psoriasis and her brother also had this disease. She was otherwise in good health. Since her disease was not controlled by the use of topical steroids, tar and dithranol, her hand psoriasis being disabling, she was considered for PUVA therapy in November 1977. After laboratory investigations, including serum liver enzymes, serum creatinine and a haematologic screening as well as test for ANA, all yielding normal values, PUVA was started. Treatments were given four times a week and consisted of an oral dose of 30 mg of 8-methoxypsoralen (Puvamet®, Draco, Sweden) and 2 hours later UVA irradiation of her palms.

During the treatment course she complained of a smarting pain in her hands, but nothing remarkable could be inspected. For this reason the irradiation periods were kept short, and after 5 weeks a maintenance treatment schedule was started although her psoriasis had improved very little.

After 4 months no further improvement was achieved and the PUVA treatment was terminated. A laboratory screening at this time was normal except for a positive ANA test. The ANA titre had increased from <1/8 (negative) to 1/64 with a nucleolar staining pattern. The clinical examination as well as additional tests including the Crithidia luciliae test (antibodies against native DNA), a blood sedimentation rate, serum electrophoresis and urine analysis were normal, and did not reveal any signs of a connective tissue disease.

Two months after the termination of the PUVA therapy she developed joint pains mainly in the fingers. The ANA titre now was 1/32 and no rheumatoid factors were detected. The joints became less painful and in August 1978 the ANA-titre was again normal (<1/8).

Her arthralgias recurred in the summer of 1979. She was hospitalized in November 1979 with 2 weeks history of increasing respiratory distress, difficulties in swallowing and fatigue. Initially pulmonary emboli were suspected but could be ruled out. Examination of her lung capacity showed a restrictive lung function decrease of 25%. A small parenchymatous infiltrate in the basal part of the left lung was visualised by X-ray. The physical examination revealed a woman with rest dyspnoe and hyperkeratotic lesions of the elbows, palms and soles. On the knuckles and the dorsa of the hands there was a slight erythema with diffuse demarcation. Swelling and erythema of the DIP joints were also noticed.

Laboratory studies showed a sedimentation rate of 30 mm, normal values for erythrocyte count, haemoglobin, WBC count with a normal differential count, serum creatinine and serum electrolytes. Serum albumine was slightly lowered, 34 g/l (normal 40–52 g/l). Serum liver enzymes showed elevations of ASAT, 1.92 μ kat/l (normal values less than 0.7 μ kat/l); ALAT, 1.5 (normal values less than 0.7 μ kat/l); lactate dehydrogenase, 20.7 μ kat/l (normal values below 8.0 μ kat/l) with elevations of fractions II and III while the levels of glutamyl transpeptidase and alkaline phosphatase were within the normal range.

Antinuclear antibodies were demonstrated in the blood at a titre of 1/512 with a nucleolar staining pattern. No antibodies against native DNA were found when investigated with the Crithidia luciliae test. Nor were any rheumatoid factors or antibodies against mitochondria, smooth muscles or kidney glomeruli found.

The symptoms of arthralgia, dyspnoe and dysphagia together with the presence of ANA with a nucleolar staining pattern suggested a diagnosis of systemic scleroderma. For this reason additional tests were performed including oesophageal manometry, which in a part of oesophagus showed aperistalsis consistent with the scleroderma diagnosis. Electromyography showed myositis mainly in the proximal muscles of the extremities. X-ray examination of joints revealed only signs of arthrosis in the DIP joints of the hands.

Table I. *Treatment course, ANA titres and collagenosis symptoms in the reported patient*

Symptoms (non psoriasis)								
ANA titre	<1/8	1/64	1/32	<1/8		1/512	1/256	
PUVA								
Month/year	11/77	2/78	4/78	8/78	8/79	11/79	1/80	3/80

A needle liver biopsy showed changes of slight steatosis. Skin biopsies from the diffusely demarcated erythema of the dorsa of the hands were examined by routine light microscopy and by immunofluorescence technique. Histologically there were slight changes of hyperkeratosis and focal parakeratosis but no indications of scleroderma. The immunofluorescence examination was negative.

The clinical picture and the results of the laboratory examinations were considered sufficient for a diagnosis of a connective tissue disease but without enough specificities for subclassification. Treatment with prednisolone, 30 mg daily, and azathioprine (Imurel®, the Wellcome Foundation Ltd) 100 mg daily, was started. The patient improved substantially and she was sent home still on this therapy.

In January 1980, one month later, she got the shivers and was therefore hospitalized again. Sepsis was suspected and after samples were taken from the throat, blood and urine for microbiological cultivations, benzyl-penicillin and gentamicin were administered systemically. After a few days the fever disappeared. The microbiological examinations did not explain the fever. The ANA-titre was 1/256 and still of the nucleolar staining pattern. Her condition was well controlled even after the doses of prednisolone and azathioprine were lowered to 10 mg and 75 mg daily respectively.

The possibility of a paramalignant phenomenon was suggested but additional investigations with regard to the presence of a malignancy were negative.

In March 1980 her condition suddenly deteriorated and she died in a pulmonary oedema followed by heart arrest. At autopsy congestive heart failure with pulmonary oedema was found to be the death cause but nothing was detected to facilitate the subclassification of the connective tissue disease. A summary of the treatment course, ANA titres and collagenosis symptoms is given in Table I.

DISCUSSION

It is not possible to answer the question whether the PUVA therapy had any etiological significance for the development of the connective tissue disease or not. No ANA were found prior to PUVA therapy but appeared with the nucleolar staining pattern during the treatment. After the termination of PUVA the ANA disappeared but returned later together with symptoms of a connective tissue disease (Table I). The staining pattern of the ANA was consistent, strongly suggesting the PUVA therapy as a factor of importance in the development of the collagen vascular disease. The PUVA therapy might have revealed or advanced the start of a latent connective tissue disease or it might even have caused it.

Sunlight may be a precipitating factor in SLE (6). The clinical features of our patient, however, were more consistent with a scleroderma-like syndrome as was the nucleolar staining pattern of the ANA (7).

PUVA therapy has been shown to promote the development of ANA (2, 3, 8) predominantly of the homogenous staining pattern (3, 8). The mechanism is not clear but there are some experimental results suggesting a theoretical basis for the antibody production. Psoralen-DNA photoadducts are immunogenic (9) and UVA light alone may induce DNA breaks (10).

The present case together with the findings of ANA during PUVA therapy increases the concern for systemic immunological effects associated with long-term PUVA therapy. As the appearance of ANA may herald the development of a connective tissue disease, monitoring for ANA is advisable in PUVA patients. The future may prove whether ANA of the nucleolar staining pattern has a more specific pathogenetic implication.

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Silent Lupus Nephritis among Patients with Discoid Lupus Erythematosus

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Roujeau JC, Belghiti D, Hirbec G, Poli F, Sobel AT, Revuz J, Touraine R. Silent lupus nephritis among patients with discoid lupus erythematosus. *Acta Derm Venereol (Stockh)* 1984; 64: 160–163.

A kidney biopsy was performed in 7 hypocomplementemic discoid lupus erythematosus patients despite the absence of overt renal involvement. Five patients had glomerular immune deposits and 2 patients with disseminated discoid lupus erythematosus exhibited definite proliferative glomerulonephritis. Those findings show that silent lupus nephritis may be encountered in discoid as well as in systemic lupus erythematosus, providing additional evidence supporting the unity of the disease. We suggest that hypocomplementemic patients with discoid lupus erythematosus must be carefully screened for renal disease by periodic urinalysis examinations. *Key words: Disseminated discoid lupus erythematosus; Hypocomplementemia; Kidney biopsy.* (Received August 27, 1983.)

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Discoid lupus erythematosus (DLE) is rarely associated with clinical kidney involvement as assessed by urinary abnormalities. For example, Dubois (1) reported abnormal urinalysis in 8% of DLE patients and in 1 out of 15 patients with disseminated discoid lupus (DDLE). Overt renal disease was considered as even less frequent by others (2). Kidney biopsies were performed in 5 DLE patients with overt renal disease (3). This study underlined the possibility of glomerular changes consistent with mild lupus nephritis indicating that multivisceral involvement may occur in so-called skin restricted lupus. On the other hand it is well known that histologically defined lupus nephritis may exist without clinical renal abnormalities. This is called "silent lupus nephritis" (4, 5).

Therefore considering the eventuality of multivisceral lupus in DLE, the possibility of silent nephritis and the recognized role of complement as a marker of systemic lupus (6), it was decided to study the kidney pathology of those patients with DLE and DDLE who exhibited hypocomplementemia. This definition selected patients at risk for glomerulonephritis, potentially severe enough to require a specific therapeutic strategy.