CLINICAL COURSE OF DRUG-INDUCED LUPUS AND IMMUNOLOGICAL PROFILE OF PATIENTS

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ABSTRACT
Drug-related-lupus (DRL) is one of the manifestations of the drug-induced lupus (DIL). The aim of the present study was to analyze the clinical and immunological characteristics of patients with DRL, in order to summarize the manifestations, which worsen the prognosis of the disease. One hundred patients with systemic lupus erythematosus (SLE) were included in the study. Patients with DRL were 10 % of all screened lupus patients. In the patients observed by us, DRL had developed after the use of Cephalosporin (Rocephin), D-penicillamine, gold salts, Procainamide, beta-blockers, vaccines. The leading clinical manifestations in these patients were cutaneous and muscular ones, respectively, necrotizing vasculitis in five patients (50 %), myositis – in three patients (30 %), and in two patients (20 %) - generalized skin reaction, toxic epidermal necrolysis (Lyell syndrome). We found antinuclear antibodies (ANA) in nine patients (90 %) with DRL.

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Introduction
Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with an indefinite etymology, diverse clinical picture and different immunological abnormalities (6, 9). DIL is a part of drug-induced autoimmunity (DIA). DIA is an immune response that is induced by certain medications and depends on various immunological mechanisms (10).

Only cases with a clear anamnestic linkage are considered as DIL (1, 8). Literature-based data analysis reveals that the incidence of DIL is between 6 % and 12 % of patients with lupus. Drugs that cause DIL are divided into two categories, according to the degree of risk (6): high-risk medications such as Procainamide and Hydralazine; and low-risk medications (<1 %), which include anticonvulsants, antipsychotics, antiarrhythmics, antihypertensives, ACE (angiotensin-converting-enzyme) inhibitors, calcium antagonists, etc., certain antibiotics (penicillins, sulfonamides, some tetracyclines, Isoniazid), antifungals, statins, biologics, thyreostatics, D-penicillamine and others.

According to different authors, DIL can develop in months or years (on average, 13 to 27 months) after the use of relevant medication. This period is called the “initial induction period”. The symptoms recede after discontinuing the use of the drugs. The drug elimination time is short, varying between a few weeks and three months. Taking drugs repeatedly over a period of time, also called “second-drug induced episode”, causes patients to develop the disease after a few days (11).

Distinctive clinical signs characterizing DIL are described (6). According to some authors (12), the clinical course of DIL varies from conditions with individual affected organs to severe systemic inflammatory conditions, dominated by manifestations of vasculitis. Systemic DIL usually is characterized by typical lupus-like symptoms, including skin signs, mild systemic involvement, and a typical laboratory profile (1, 6).

An association with antibodies against histone protein components involved in the nuclear chromatin structure is established in DIL (2, 3). Nearly 50 % of DIL cases are positive for anti-single-stranded DNA (anti-ssDNA) antibodies. Some authors have established antiphospholipid antibodies (APL) - anticardiolipin antibodies (ACL) in approximately 75 % of the patients with DIL, with a low percentage of thrombosis in these patients (4).

The aim of the present clinical study was to determined the incidence of DIL in patients with lupus, to analyze the clinical and immunological characteristics of the patients with DIL, and to summarize the manifestations of DIL which worsen the prognosis of the disease.

Materials and Methods
One hundred patients with SLE were included in the present study. All patients were diagnosed and treated over several years at the Clinic of Rheumatology, St. Ivan Rilski University Hospital (Sofia, Bulgaria). The diagnosis criteria for SLE published by the American College of Rheumatology (ACR) in 1982 were used to make the diagnosis. All patients included in the study gave a written informed consent.

Various diagnostic methods were used to make the diagnosis SLE: Skin: Lupus Band Test, done upon a standard skin biopsy; Musculoskeletal/Locomotor System: skin and muscle biopsy, different imaging methods; Lungs: conventional radiography, computed tomography with high-resolution equipment, lung scintigraphy, and pulmonary function evaluation test through pulmonary diffusion; Heart: echocardiography; holter monitor for the presence of rhythm and conduction disorders; Vessels: large-vessel Doppler ultrasonography, capillaroscopy, biopsy, and angiography in multiple vascular incidents; Kidneys: ultrasonography to determine the size and structure of the parenchyma, renal

TABLE 1

Patients with DIL

No.	Patient	Cause	Clinical manifestation	Immunology	Result
1	Age: 34 Female	Gold salts in Rheumatoid Arthritis (RA) with lupus immunology	Necrotizing vasculitis affecting the whole body with necroses, including the lips	ANA (+) RF (+)	Controlled, the necroses vanished without a trace
2	Age: 30 Female	Rocephin	Febricity, pleurisy, leucopoenia in presence of SLE	ANA (+) RF (-)	Remission occurred by discontinuing the use of the medication
3	Age: 33 Female	Hepatitis B Vaccine	Hypersensitive necrotizing vasculitis affecting the whole body with central necroses	ANA (+) RF (-)	Controlled, the necroses vanished without a trace after appropriate treatment
4	Age: 47 Male	Procainamide	Necrotizing vasculitis affecting the whole body, evidence of subclinical lupus	ANA (+) RF (-)	Controlled, the necroses vanished without a trace after appropriate treatment
5	Age: 55 Female	Penicillin group antibiotic	Severe myositis, subsequent – SLE+PSS overlap syndrome	ANA (+) RF (+)	Controlled by corticosteroids and Methotrexate, discontinuing the use of the medication
6	Age: 42 Female	Penicillin group antibiotic	Epidermolysis Bullosa (EB) + severe vasculitis subsequent SLE with secondary antiphospholipid syndrome + Rheumatoid arthritis (RA)	ANA (+) RF (+) ACL (+)	Controlled, vasculitis occurs with multiple infarcts
7	Age: 42 Female	Penicillin group antibiotic	Lyell syndrome + myositis, subsequent polymyositis (PM) with lupus immunology	ANA (+) RF (-)	Patient treated in Burns Unit
8	Age: 42 Female	Obsidan (Propranolol)	Necrotizing vasculitis, subsequent SLE	ANA (+) ACL (+)	Lethal outcome
9	Age: 55 Female	Cuprenil (D-Penicillamine)	Myositis, subsequent SLE + PSS	ANA (+) ACL (+) TAT (+) MAT (+)	Controlled by discontinuing the use of the medication
10	Age: 53 Male	Influenza Vaccine	Myositis, demyelinating polyneuropathy (Guillain-Barré Landry syndrome)	ANA (+) RF (-) ACL (+)	Lethal outcome

TABLE 2

Incidence of clinical symptoms and immunological abnormalities in patients with the DIL and SLE

Clinical signs	**DRL Incidence (n = 10)**	**Incidence in a common group (n = 100)**	P
Necrotizing vasculitis	5 (50 %)	23 %	n.s.
Myositis	3 (30 %)	15 %	n.s.
Demyelinating polyneuropathy (Guillain-Barré) Landry syndrome)	1 (10 %)	0.28 %	$P < 0.05$
Generalized skin reaction (Lyell syndrome)	2 (20 %)	0.57 %	$P < 0.05$
ANA (+)	9 (90 %)	94 %	n.s.
ACL (+)	7 (70 %)	81.25 %	n.s.
Antihistone antibodies	1 out of 4 patients tested (25 %)	36 %	n.s.

n.s.: non-significant ($P > 0.05$)

puncture biopsy; Nervous System: electroencephalography, fundoscopy, MRI with Fluid Attenuating Inversion Recovery (FLAIR) pulse sequence for skin lesions in cerebrovasculitis; electroneuromyography; CT scan with intravenous contrast for identifying vascular anomalies; Immunological Studies: Antinuclear antibodies (ANA), anticardiolipin antibodies (ACL) and antihistone antibodies; Study of rheumatoid factor. All serum samples were screened for antinuclear antibodies (ANA) by indirect immunofluorescence. Sera were tested by enzyme linked immunosorbent assay for ACL and antihistone antibodies. The test was performed with an automatic analyser Alegria, ORGANTEC (Diagnostica GmbH, Mainz, Germany).

The results were processed by SPSS statistical program. Values of $P < 0.05$ were accepted as statistically significant.

Results and Discussion

The patients with DIL were 10 % of the lupus population, which is consistent with the findings reported in the literature. The DIL syndrome had developed after the use of antibiotics from the penicillin group, such as Cephalosporin (Rocephin) and D-penicillamine, gold salts, Procainamide, beta-blockers, vaccines. Details about the patients with DIL are presented in **Table 1**.

The main clinical manifestations in the patients diagnosed with DIL were cutaneous and muscular. Five patients (50 %) were diagnosed with necrotizing vasculitis, three patients (30 %) with myositis, and two patients (20 %) with generalized skin reaction (Lyell syndrome). One patient was diagnosed with demyelinating polyneuropathy – Guillain-Barré-Landry syndrome. Immunological abnormalities were detected: antinuclear antibodies in nine patients (90 %), anticardiolipin antibodies (ACL) in four patients (40 %), antihistone antibodies in one out of four patients tested (25 %).

The incidence of symptoms and immunological profile in patients with DIL and SLE, as well as a comparison between the two groups are presented in **Table 2**. The results showed that, in the observed patients, DIL developed on a rheumatoid basis with lupus immunology under the influence of the above-mentioned drugs.

All patients were with arthralgia (except arthritis). According to some authors, drug-induced lupus syndromes generally have various mild cutaneous manifestations (6). Other authors describe DIL occurring with severe systemic inflammatory response dominated by manifestations of vasculitis (12). In our study, some of the manifestations of DIL were associated with a severe hypersensitivity reaction of the skin, muscles, and the nervous system. Regarding the skin manifestations, vasculitides with Lyell syndrome were observed as well. Involvement of the nervous system was observed in one patient, who was diagnosed with demyelinating polyneuropathy that had developed after influenza vaccine application.

At this stage, a strongest relationship is established between DIL and antihistone antibodies. These antibodies are reported to be detected in approximately 75 % of the patients with DIL (6) but in our study the percentage was only 25 %. Presently, it is not clear whether these antibodies usually precede the development of DIL or are derived from it.

About 70 % of the patients with DIL are commonly reported to have positive tests for antiphospholipid (APL) antibodies (4). Most authors consider APL conditionally non-pathogenic. However, there are reports of thrombotic manifestations in patients with DIL (1, 5, 7). In our study we carried out tests for one type of APL anticardiolipin antibodies and 40 % of the patients showed positive tests results. Regarding the clinical course of the disease, we observed vasculitis with multiple infarcts in one patient. Wilk (12) found antineutrophil cytoplasmic antibodies, anti-β2-GPI antibodies and antihistone antibodies in a group of patients with DIL accompanied by manifestations of vasculitis, and suggested that these antibodies could be used as a diagnostic marker for DIL with dominant vasculitic manifestations.

The large percentage of DIL patients (90 %) with detected antinuclear antibodies in our study corresponded well with literature-based data that a high percentage of patients with DIL have positive tests for (anti-ssDNA) antibodies, which is a non-specific immunological marker (6). Further research of a larger group of patients with DIL is needed in order to establish the clinical and immunological characteristics of patients with DIL.

Conclusions

In our study the manifestations that worsened the DIL disease prognosis and could be considered a cause of death were necrotizing vasculitis and nervous system injuries such as polyneuritis with ascending respiratory paralysis. To the observed immunological abnormalities included: antinuclear antibodies in nine our of ten patients, anticardiolipin antibodies in four out of ten patients, and antihistone antibodies in one out of four patients.

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