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D-penicillamine-induced lupus erythematosus as an adverse reaction of treatment of Wilson's Disease

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To the Editors

Wilson's Disease (WD) is an autosomal recessive disorder of copper metabolism characterised by pathological copper accumulation, particularly in the liver and brain [1]. There is a wide spectrum of clinical symptoms, but most often the hepatic and/or neuropsychiatric phenotypic presentation of WD predominates [1]. Of note, WD can be successfully treated with pharmacological agents, resulting in a negative copper balance. Currently, two groups of drugs are used: 1) chelators [d-penicillamine (DPA) or trientine (TN)], which increase urinary copper excretion; and 2) zinc salts, which decrease copper absorption from the digestive tract [1]. Long-term studies have documented positive outcomes in almost 85% of correctly treated patients. For treatment success, lifelong treatment is necessary, requiring ongoing monitoring for efficacy and adverse events [1]. Failure to comply with lifelong therapy can lead to recurrence and liver failure. In addition, therapeutic success relies on early diagnosis, which may be challenging [1]. Diagnosis must be confirmed in experienced WD centres by clinical, laboratory and genetic studies. There are several pitfalls en route to a correct WD diagnosis, and physicians must be aware that even the presence of two confirmed pathogenic mutations may not establish such a diagnosis, because both mutations may be localised on one allele (uniparental isodisomy). In situations where results diverge, a ^{64}Cu radioactive copper incorporation test can be performed [2].

DPA, developed in 1956 by John Walshe, is still the most frequently used treatment, with probably the best, and longest, experience [1]. However, DPA can be responsible for a number of potentially important adverse drug-related events (ADRs) (Tab. 1) [3]. Because of this, the safety of DPA treatment should be closely monitored, not only at initiation, but also throughout the duration of treatment.

We present the case of a 32-year-old man who had initially been diagnosed with an anxiety syndrome aged 23 and treated with several medications (sertraline, paroxetine, and ultimately a combination of escitalopram and chlorproxiten) with minimal benefit. After eight years, he reported abdominal pain, and after diagnostic tests [liver function test (LFT): ALT (31 U/L, normal: 10-40 U/L), AST (27 U/L, normal: 10-40 U/L), GGTP (156 U/L, normal: 7-64 U/L)], oesophageal varices in gastroscopy, and picture of liver cirrhosis in abdominal ultrasound), compensated liver cirrhosis was diagnosed (Child-Pugh class A). The triggers of cirrhosis, infectious (viral) and autoimmune disorders were excluded. Based on the hepatic and psychiatric symptoms, abnormal results of copper metabolism (low serum ceruloplasmin (17.4 mg/dL, normal: 25-45 mg/dL); increased urinary copper excretion (145 µg/24 hours, normal: 0-50 µg/24 hours), the presence of a Kayser-Fleischer ring (Fig. 1), and genetic

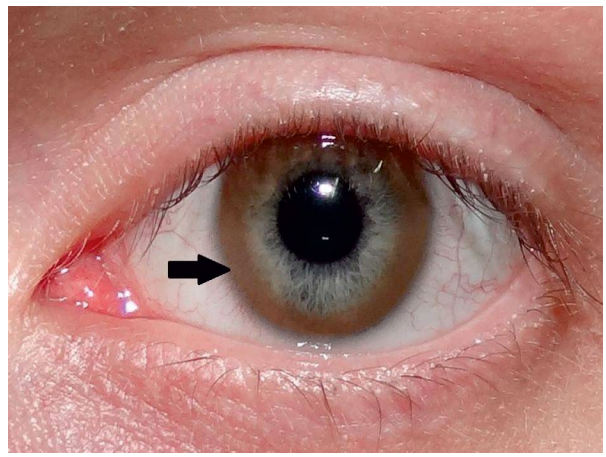

Figure 1. Kayser-Fleischer ring (black arrow) (clinic archives)

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Table 1. Possible adverse drug reactions (ADRs) due to d-penicillamine and their classifications according to time of onset (early/late) [3]

Affected system	Symptoms	Time of ADR onset (early/late)
Skin	**Degenerative dermatoses** [elastosis perforans serpiginosa, cutis laxa (skin laxity), anetoderma, pseudo-pseudoxanthoma elasticum]	Late
	Bullous dermatoses (pemphigus and bullous disease)	Early
	Miscellaneous cutaneous conditions	
	— lichen planus-like eruptions, aphthous stomatitis or glossitis, oral ulcerations	Early
	— alopecia, psoriasiform dermatitis, seborrheic dermatitis-like picture, hair falling out, yellow-nail syndrome	Late
Nervous system	Paradoxical neurological deterioration,	Early/late
	Myasthenia-like syndromes,	Late
	Peripheral sensory-motor neuropathies,	Late
	Optic nerve neuropathy,	Late
	Serous retinitis,	Late
	Hypogeusia (diminution in taste perception),	Late
	Deafness	Late
Connective tissue disease	Lupus-like syndrome,	Late
	Polymyositis,	Early/late
	Arthralgia,	Early/late
	Rheumatoid arthritis	Late
Renal	Proteinuria,	Early/late
	Haematuria,	Early/late
	Goodpasture syndrome,	Late
	Severe fatal glomerulonephritis associated with intra-alveolar haemorrhage,	Late
	Renal vasculitis	Late
Respiratory	Bronchiolitis,	Late
	Pulmonary fibrosis,	Late
	Pneumonitis,	Late
	Pleural effusion,	Late
	Dyspnoea	Late
Gastrointestinal	Nausea,	Early/late
	Vomiting,	Early/late
	Diarrhoea,	Early/late
	Cholestatic jaundice,	Late
	Liver siderosis	Late
Haematological	Thrombocytopenia,	Early/late
	Neutropenia,	Early/late
	Agranulocytosis,	Late
	Aplastic anaemia,	Late
	Haemolytic anaemia	Early/late
Immunological	Immunoglobulin deficiency	Late
Reproductive system and breast disorders	Breast enlargement	Late

Early = during first three weeks of treatment; *Late* = between three weeks and a few years of treatment

analysis (homozygous mutation c.3207C>A in the *ATP7B* gene), a diagnosis of WD was established.

Treatment with DPA was initiated, and the dose titrated to 1,500 mg daily. A year later, the patient reported fever up to 39°C with arthralgia of the shoulders, hips, knees, foot, and thoracic spine, which had led to impaired mobility. In chest X-rays, pleuritis with hydrothorax was found, an increased level of C-reactive protein (161 mg/L, normal: 0-5 mg/L) and an erythrocyte sedimentation rate of 40 mm/h (normal: 0-10 mm/h) were noted. Blood and urine microbiological analysis was performed and empirical intravenous antibiotic treatment was introduced, as well as naproxen for the symptomatic treatment of arthralgia. After receiving negative microbiological analysis of blood and urine, antibiotics were stopped. Rheumatoid arthritis was excluded (negative serum rheumatoid factor, no typical changes in joint X-rays). To exclude bone marrow disease, the patient had a biopsy that documented only stimulation of granulopoiesis, with decreased ratio of erythroid cells, probably as a drug-induced change. Additional blood analyses demonstrated the presence of lupus anticoagulant and antinuclear antibodies (ANA) titres, while anti-dsDNA, c-and p-ANCA, and CCP antibodies were negative.

Based on the clinical picture and laboratory results, a diagnosis of drug-induced lupus erythematosus (DIL) due to DPA was established [4, 5]. Despite the complication of WD

treatment, there was no deterioration of copper metabolism (urinary copper excretion (170 μg/24 hours)], LFT (ALT 34 U/L, AST 27 U/L, GGTP (29 U/L), nor symptoms of liver cirrhosis decompensation (Child-Pugh class A). The patient did not present new hepatic or neurological WD symptoms, although the K-F ring persisted due to the short duration of anti-copper treatment. DPA was stopped, and zinc sulphate was introduced (160 mg of elementary zinc). Symptomatic steroid treatment with oral methylprednisolone 16 mg was started, with gradual dose reduction over seven weeks.

During the first week of treatment, most of the symptoms (pain, fever) gradually diminished, and eventually disappeared. After one month, ANA were negative. During four years of follow-up, the patient has remained free of any lupus erythematosus (LE) symptoms. The patient did not present any new WD symptoms, liver cirrhosis remained stable (Child-Pugh class A), LFTs were in normal range (ALT 39 U/L, AST 28 U/L, GGTP 23 U/L), copper metabolism showed adequate decoppering treatment [serum ceruloplasmin 12.6 mg/d, urinary copper excretion < 45 μg/24 hours (< 100 μg/24 hours documents the correct anti-copper treatment according to the European Association for Study of the Liver)], the K-F ring disappeared (the K-F ring usually disappears during 3-5 years of treatment), and he regularly took zinc sulphate, paroxetine, chlorproxiten and escitalopram.

DIL, firstly described by Hoffmann in 1945 after sulfadiazine, is a lupus-like autoimmune disorder caused by different pharmacological agents, and comprises 6-12% of all LE cases [5]. Currently, more than 100 medications are documented as DIL triggers, including DPA [5]. DPA-DIL is a rare complication of DPA treatment first described in WD by Walshe in 1981 [5]. As classical LE, it can be classified as: 1) systemic DIL (mainly arthralgia, myalgia and serositis); or 2) subacute cutaneous DIL; or 3) chronic cutaneous DIL (with skin lesions) [4, 5].

There are no generally accepted criteria, but a DIL diagnosis is mainly based on: 1) clinical and serological symptoms of LE (at least one symptom); 2) continuing exposure to the drug; 3) no history suggestive of LE before treatment with the specific drug; 4) exclusion of other disorders (mainly autoimmune and infectious); and 5) resolution of clinical symptoms within weeks (or months) after medication withdrawal [4, 5]. The presence of ANA is supportive of the diagnosis; however, its absence does not exclude such a diagnosis, especially if other antibodies related to LE are present [5]. The presence of low positive ANA titres in the general population does not necessarily indicate the diagnosis of autoimmune disease.

Management of DIL includes discontinuation of the causative drug, and treatment with steroids and non-steroid anti-inflammatory drugs in more severe cases. Generally, the prognosis is good if DIL is correctly and promptly diagnosed, as in our case [5].

As mentioned previously, DPA is an effective, recommended and often-used drug in the treatment of WD [1]. However, DPA is also a significant contributor to the number of ADRs that may lead to treatment discontinuation in 15–30% of patients. ADRs can be categorised as either early reactions, occurring during the first three weeks after treatment introduction, or late reactions, occurring after three weeks to several years of treatment, including DIL (Tab. 1) [3].

Using our case as an example, we would like to emphasise that knowledge of ADRs related to anti-copper treatment is crucial for physicians and patients [1]. When DPA is used for WD, DPA-DIL should always be taken into account, especially during the first year of treatment if the patient complains of arthralgia, fever and/or the symptoms of renal injury.

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