Digestive and Liver Disease 51 (2019) 1741–1743

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Correspondence

D-penicillamine-induced autoimmune disorders

Dear Editor

D-penicillamine remains a cornerstone of copper chelation therapy in Wilson's disease, an inherited autosomal recessive disorder, which results in impaired biliary copper excretion and accumulation of copper in plasma and tissues, preferentially in the central nervous system and liver. Safety of the drug is under debate because many case reports have described severe adverse events, leading to the discontinuation of therapy [1]. D-penicillamine can induce variable immune-related disorders, including antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. The exact mechanisms of D-penicillamine-induced autoimmunity are still unknown. Of note, pre-existing autoimmune diseases can be present prior to the initiation of treatment in approximately 5% of patients with Wilson's disease [2].

Since 1988, we follow 180 patients with Wilson's disease (118 females and 62 males, mean age 28.2 ± 7,8years), 174 of whom were treated with D-penicillamine from 2 months to 46 years (mean 6.3 ± 5.9). Six patients received a liver transplant for progressive liver failure. We retrospectively studied medical charts of patients to evaluate clinically significant adverse events, which were probably, possibly or definitely related to D-penicillamine therapy. The most common drug-induced reactions were hematological abnormalities, variable kidney disorders, including nephrotic syndrome, and skin lesions, particularly urticaria (Table 1). A fever above 39 °C was noted in two patients after each attempt of taking the medication (250 mg) and required discontinuation of the drug. During D-penicillamine treatment only four patients, including three females and one male, developed overt autoimmune disorders, such as interstitial lung disease, drug-induced lupus or ANCA-associated vasculitis. The incidence of autoimmune adverse events was similar in males and females (2.7% and 1.7%, respectively). The fatal case of systemic vasculitis deserves particular attention, since there are few previous reports of D-penicillamine-induced seropositive ANCA-associated vasculitis with both renal and pulmonary involvement [3–5].

A 37-year-old female was admitted to our nephrology department with a 3-week history of dialysis-dependent renal failure, hemoptysis and severe anemia. Three years earlier, Wilson's disease was diagnosed based on Child A liver cirrhosis, tremor, low serum ceruloplasmin level, and Kayser-Fleischer rings. Treatment with D-penicillamine at a dose of 750 mg/daily and zinc sulfate was started. The therapy was well tolerated and resulted in improvement of the neurological symptoms, liver cirrhosis was compensated well. In March 2018, laboratory findings showed anemia, hematuria, trace proteinuria and a moderate decrease in renal function. In August 2018, hemoglobin level dropped to 45 g/L, and serum creatinine increased up to 680 μmol/L. She was treated with hemodialysis and blood transfusions. In September 2018, the patient developed a fever and hemoptysis and was referred to our clinic. On admission, she presented with proteinuria of 1 g/24 h, microhematuria with erythrocyte casts, severe anemia (hemoglobin 58 g/L), myeloperoxidase-ANCA (122.8 IU/mL, normal range 0–5), and positive antinuclear antibodies (1:640). Chest computed tomography showed diffuse bilateral interstitial changes and consolidation (Fig. 1). Platelet count, haptoglobin and lactate dehydrogenase levels were within the reference ranges. Testing for anti-glomerular basement membrane antibodies, anti-DNA antibodies, cryoglobulins, monoclonal gammapathy,

Table 1
D-penicillamine-induced adverse events in 174 patients with Wilson's disease (114 females, 60 males).

Event	n (%), gender	Male (%)	Female (%)
Thrombocytopenia <150 × 10^9/L	84 (48.3)	27 (45.0)	57 (50.0)
Leukopenia <4.0 × 10^9/L	46 (24.6)	14 (23.3)	32 (28.1)
Hematuria	12 (7.0)	3 (5.0)	9 (7.9)
Nephrotic range proteinuria	5 (2.9)	3 (5.0)	2 (1.8)
Tubular interstitial nephritis	9 (5.0)	3 (5.0)	6 (52.6)
Skin lesions	8 (4.6)	4 (6.6)	4 (3.6)
Urticaria	6 (3.4)	3 (5.0)	3 (2.6)
Localized scleroderma	1 (0.6)	0 (0.0)	1 (0.9)
Papular rash	1 (0.6)	1 (1.7)	0 (0.0)
Fever above 39 °C	2 (1.1)	2 (3.3)	0 (0.0)
Systemic lupus erythematosus	2 (1.1)	0 (0.0)	2 (1.8)
Interstitial lung disease	1 (0.6)	1 (1.7)	0 (0.0)
ANCA-associated vasculitis	1 (0.6)	0 (0.0)	1 (0.9)

Note: Any adverse events that were probably or definitely related to D-penicillamin.

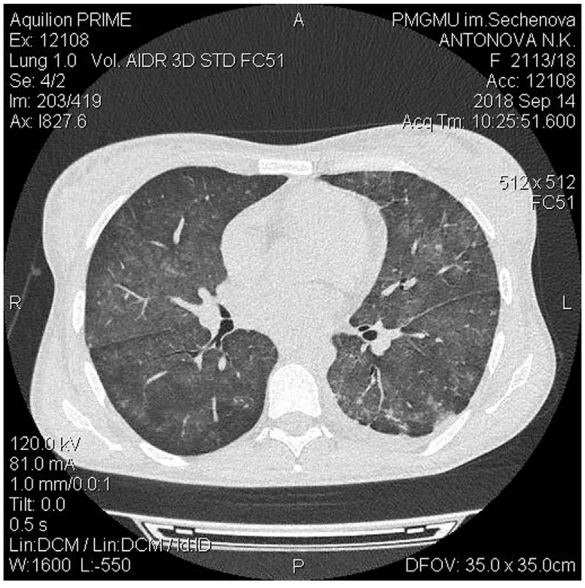

Fig. 1. Chest computed tomography showing diffuse bilateral interstitial disease.

https://doi.org/10.1016/j.dld.2019.08.025
1590-8658/Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l.

and markers of antiphospholipid syndrome was negative. Renal biopsy was not performed due to severe anemia. The patient was given a diagnosis of ANCA-associated microscopic polyangiitis, rapidly progressive glomerulonephritis, and diffuse intra-alveolar hemorrhage that we attributed to D-penicillamine treatment. D-penicillamine was discontinued. Immunosuppressive treatment with three methylprednisolone daily pulses (750 mg/d), followed by 48 mg/d of methylprednisolone orally, and two cyclophosphamide pulses (10 mg/kg) alleviated hemoptysis and fever, reduced myeloperoxidase-ANCA and antinuclear factor titers, and increased hemoglobin level up to 101 g/L without erythrocyte transfusions. Nevertheless, kidney function did not recover. Cyclophosphamide administration was complicated by leukopenia, thrombocytopenia, and nosocomial pneumonia that resolved after antibiotics and intravenous immunoglobulin. We planned to start rituximab administration. However, the patient developed fatal respiratory infection within two weeks after discharge from the clinic.

Our findings suggest that serious immune-related adverse events are relatively infrequent in Wilson's disease patients receiving a long-term treatment with D-penicillamine. Nevertheless, D-penicillamine can induce a severe and even lethal ANCA-associated vasculitis with both rapidly progressive kidney failure and diffuse intraalveolar hemorrhage that requires discontinuation of D-penicillamine and immediate and aggressive immunosuppressive treatment.

Funding

"Russian Academic Excellence Project 5-100".

Conflict of interest

None declared.

Patient consent

Not required.

References

[1] Weiss KH, Thurik F, Gotthardt DN, Schäfer M, Teufel U, Wiegand F, et al. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. Clin Gastroenterol Hepatol 2013;11(8):1028–35.
[2] Seessle J, Gotthardt DN, Schäfer M, Gohdes A, Pfeiffenberger J, Ferenci P, et al. Concomitant immune-related events in Wilson disease: implications for monitoring chelator therapy. J Inherit Metab Dis 2016;39:125–30.
[3] Sternlieb I, Bennet B, Scheinberg IH. D-Penicillamine-induced Goodpasture's syndrome in Wilson's disease. Ann Intern Med 1975;82:673–6.
[4] Bienaimé F, Clerbaux G, Plaisier E, et al. D-penicillamine-induced ANCA-associated crescentic glomerulonephritis in Wilson disease. Am J Kidney Dis 2007;50:821–5.
[5] Sharma R, Jain S, Kher V. ANCA-associated Goodpasture's syndrome in a patient with rheumatoid arthritis on penicillamine. Indian J Nephrol 2012;22:45–7.

Teona Rozina [a,b]
[a] *Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russian Federation*
[b] *Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russian Federation*

Saglara Fastovets [*]
Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russian Federation

Olga Lee
Agunda Kuchieva
Nikolai Bulanov
Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russian Federation

Sergey Moiseev [a,b]
[a] *Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russian Federation*
[b] *Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russian Federation*

[*] Corresponding author at: Tareev Clinic of Internal Diseases, Rossolimo, 11-5, Moscow, 119435, Russian Federation.
E-mail address: s.v.fastovets@gmail.com (S. Fastovets)

25 April 2019

Ready, get set, go: Fast preoperative genetic diagnosis is the present future in Lynch syndrome surgical strategy

Dear Editor,

Lynch syndrome (LS) is an autosomal dominant hereditary cancer predisposition syndrome caused by pathogenic germline variants in DNA mismatch repair genes (MMR) *MLH1*, *MSH2*, *MSH6* and *PMS2*. LS accounts for 3–5% of all colorectal cancers (CRC). LS associated CRC generally has microsatellite instability and lacks for MMR protein expression. The risk of CRC in LS patients is between 10 and 82% depending on the involved MMR gene. LS patients are at high risk to develop synchronous/metachronous cancer both colonic and extracolonic (e.g. endometrial, urothelial and ovarian) [1]. The risk of metachronous CRC is 62%, 30 years after surgery [2]. The optimal surgical treatment of CRC in LS is still debated. Extended resection, depending on clinical and molecular scenario, should be considered not only for primary CRC treatment but especially for prevention of metachronous CRC. Diagnosis for LS is molecular. However, germline genetic testing is performed postoperatively in the majority of cases, missing a possible important role in preoperative evaluation and surgical planning.

A 22-year-old female patient, after evidence of chronic anemia, was submitted to thorax-abdomen CT scan with evidence of a right colon neoplasm. Subsequent colonoscopy identified two lesions: a 8 cm stenosing neoplasm of the proximal portion of the right colon and a 3 cm sessile neoplasm in the caecum. The former was a moderately differentiated adenocarcinoma while the latter a tubulo-villous adenoma with focal areas of high-grade dysplasia. In the suspect of a LS, immunohistochemistry (IHC) testing for MMR was performed on the endoscopic biopsy with evidence of *MLH1* and *PMS2* protein lack of expression. Following genetic testing results were available within 7 days with identification of the pathogenic variant c.522_523dupGA (p.Lys175Argfs*28) in *MLH1*. After a detailed genetic and surgical counselling, the patient was submitted to laparoscopic total colectomy with ileo-rectal anastomosis. The neoplasm was a pT2 N0 Mx G3 adenocarcinoma. Discharge was on 6th postoperative day in optimal clinical conditions. Six months follow up was uneventful with a reported good quality of life.

Timing of LS diagnosis is critical in CRC patients because early diagnosis could guide the surgical strategy (extended versus segmental resection). However, diagnosis of LS is usually achieved postoperatively even a long time after surgery. Because LS accounts for 3–5% of CRC, IHC for MMR and/or microsatellite instability testing (MSI) are recommended in all CRCs [1]. Two studies