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CASES WITH A MESSAGE

Cyclophosphamide-induced severe acute hepatitis in a rheumatic disease: case-based review

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Abstract

In rheumatology practice, the risk of hepatotoxicity from medications, including non-steroidal anti-inflammatory drugs, notably, and methotrexate, sulfasalazine, leflunomide, and azathioprine is highly recognized by the rheumatologists. On the other hand, hepatotoxicity is neither a commonly expected nor a well-known side effect of cyclophosphamide (CYC) which is particularly used for vital organ involvements in systemic lupus erythematosus (SLE) and systemic vasculitis. Here we reported a 19-year-old case of SLE who, while on oral CYC treatment of 100 mg/day, was detected to have asymptomatic liver enzyme elevation and then developed acute hepatitis due to intravenously administered high-dose (1 g) CYC for neuro-lupus. Results of liver biopsy indicated drug-related toxicity. We discussed here with the other, although rare, cases available in the literature with an attempt to highlight the risk of hepatotoxicity and acute hepatitis due to CYC.

Keywords Cyclophosphamide · Hepatotoxicity · Severe acute hepatitis · Lupus

Introduction

Anti-rheumatic agents are frequently used during the course of a plethora of disorders in rheumatology practice. Either as monotherapy or through drug–drug interactions, anti-rheumatic drugs are prone to cause hepatotoxicity. They may lead to various hepatotoxicity-related outcomes in a range from acute injury to chronic liver disease and autoimmune hepatitis. Among the widely used medications with a risk of potential hepatotoxicity, non-steroidal anti-inflammatory drugs (NSAIDs) rank up-front. Acute liver injury may also occur secondary to other drugs, namely, sulfasalazine, leflunomide, and azathioprine, and methotrexate (MTX) may result in chronic liver injury as a consequence of the interaction among drugs, host and environmental factors. From the class of biological agents, tumor necrosis factor-alpha inhibitors (particularly, infliximab) may typically be responsible for drug-induced hepatitis. Due to the varying results of animal and human studies, primary protection requires knowledge of risk factors underpinning the hepatotoxicity and considering the benefit/risk ratio of the drug to be administered [1, 2].

Cyclophosphamide (CYC) is an alkylating agent administered as a high-dose intravenous (IV) pulse therapy for neuropsychiatric symptoms and serious and/or life-threatening symptoms of SLE. As a potent immunosuppressant, CYC is in widespread use in rheumatology practice not only for SLE but also for systemic vasculitis especially in case of major/vital organ involvements with most frequently expected and well-known adverse effects of gonadal dysfunction, increased incidence of infections, hematological side effects, teratogenicity, bladder cancer, hair loss, hemorrhagic cystitis, and nausea/vomiting. Hepatotoxicity could be expected at doses delivered for the purpose of preparation for bone marrow transplantation (2–4 g/m^2), whereas at immunosuppressive doses (500–1000 mg/m^2/once a month)

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hepatotoxicity is indeed not a commonly anticipated side effect [3]. CYC-induced severe acute hepatitis is far more infrequently reported [4–11]. In this paper, we report a case who, while on CYC (100 mg/day), firstly experienced asymptomatic/mild hepatotoxicity but then, subsequent to high-dose (1 g) IV administration, developed severe acute hepatitis to point out CYC may cause hepatotoxicity and severe acute hepatitis, although rarely. In addition, a discussion about the possible mechanisms behind the CYC-induced hepatotoxicity has been provided through the review of rare cases reported previously.

Case presentation

A 19-year-old female patient presented to another hospital with headache and right-sided hemiparesis. During the first admission (31 January 2018), pancytopenia in complete blood count [hemoglobin (Hb): 9.3 g/dL, white blood cell count (WBC): 2500/mm^3, absolute lymphocyte count (ALS): 700/mm^3, platelet count (PLT): 65.000/mm^3] and hyper intense foci at thalamus in cerebral magnetic resonance imaging (MRI) imaging were determined. Cerebrospinal fluid examination was not performed due to thrombocytopenia. At that time, workout showed antinuclear antibody (ANA) (+), anti-ds-DNA positive, complement (C3) normal, and C4 was low. Liver transaminases and urinalysis were within normal limits. Thereupon, the patient was considered as SLE according to the 1997 SLE classification criteria and was given pulse-1 g/day of methylprednisolone 3 days followed by 1 mg/kg of methylprednisolone. After 12 days oral CYC started as 100 mg day (12 February 2018). The patient was referred to our rheumatology department for further evaluation. On her first admission on March 26, 2018, she had no complaint except for headache and right-sided hemiparesis. Laboratory findings were as follows: Hb: 12.2 g/dL, WBC: 4900/mm^3, PLT: 219.000/mm^3, erythrocyte sedimentation rate (ESR):9 mm/hour, C-reactive protein (CRP): 3.7 mg/L (0–5), ANA:1/1000-1/3200 positive and speckled, anti-dsDNA 52 (16–24 IU/mL), C3: 96.6 (90–180 mg/dL), C4: 14.5 (16–38 mg/dL), anticardiolipin immunoglobulin (Ig)G and IgM negative, lupus anticoagulant negative, aspartate aminotransferase (AST): 47 U/L, alanine aminotransferase (ALT): 98 U/L, lactate dehydrogenase (LDH): 419 U/L, alkaline phosphatase (ALP): 43 U/L, gamma glutamyl transferase (GGT): 24 U/L, total protein: 7.32 g/dL, total bilirubin: 0.33 mg/dL, direct bilirubin: 0.15 mg/dL. Due to elevated results in liver function test (LFT), ongoing medications of the patient other than methylprednisolone were discontinued including CYC, calcium + vitamin D, and proton pump inhibitor. When patient was queried regarding any other causes of hepatotoxicity, she reported no consumption of herbal remedies or alcohol. Ongoing methylprednisolone 32 mg treatment was sustained. Autoimmune hepatitis or toxic hepatitis was considered for the patient. She had normal levels of immunoglobulins, and all other tests for detailed hepatitis markers (hepatitis A, E, B, and C), toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, Epstein–Barr virus, as well as antimitochondrial antibody, anti-*Saccharomyces cerevisiae* antibody, liver-soluble antibody, and liver kidney microsomal antibody were negative. During the follow-up, ALT, AST, ALP, GGT and total/direct bilirubin levels of the patient reached, respectively, up to 360 U/L, 126 U/L, 52 U/L, 64 U/L, and 0.33/0.11 mg/dL as a maximum (Day 7 of CYC discontinuation). Meanwhile the patient was examined in terms of SLE organ involvements. Cerebral imaging showed hyper intense foci at thalamus which were interpreted in favor of neuro-lupus. Therefore, IV CYC infusion was planned for the patient. ALT level regressed down to 293 U/L. Despite the mild regression, liver enzyme levels remained to be high and the patient was discharged to home, arranged with follow-up checks. When re-studied 2 weeks later, AST and ALT levels returned to normal levels. The patient was delivered IV CYC 1 g. The patient re-admitted 20 days later, complaining of jaundice, abdominal distension, and abdominal pain. Test results were Hb: 13.6 g/dL, WBC: 3700/mm^3, PLT: 96.000/mm^3, ESR: 9 mm/h, CRP: 4.9 mg/L, AST: 1379 U/L, ALT: 1491 U/L, LDH: 652 U/L, ALP: 162 U/L, GGT: 231 U/L, total bilirubin:3.76 mg/dL, direct bilirubin: 3.38 mg/dL, prothrombin time (PT): 13.203, INR: 1.2, partial thromboplastin time (PTT): 34.12, and fibrinogen: 291 mg/dL. According to the LFTs, hepatocellular pattern of liver injury was considered rather than cholestatic or mixed hepatocellular—cholestatic damage. During her follow-up, the patient's INR level increased up to 1.3, fibrinogen reduced down to 173 mg/dL, and bilirubin levels elevated up to 9.05/8.0 mg/dL. Although toxic hepatitis could not be eliminated, the patient's methylprednisolone dosage was escalated to 1 mg/kg due to the possibility of autoimmune hepatitis. *N*-Acetylcysteine (NAC) and ursodeoxycholic acid (UDCA) was initiated for the likely toxic hepatitis. Hepatomegaly and splenomegaly were detected in abdominal ultrasonography. Liver biopsy showed hydropic change of hepatocytes, ballooning degeneration of hepatocytes, remarkable lobular infiltration predominantly with neutrophils, sporadic eosinophils in the portal area, piecemeal necrosis, bile ductules proliferation and cholestasis in some portal areas (Figs. 1, 2). Similar to the liver enzyme test results, liver biopsy findings also revealed predominantly hepatocellular liver injury. The patient was accepted as CYC-related acute hepatitis (toxic hepatitis). On Day 20, the patient's AST and ALT values and bilirubin levels regressed. INR value reverted back to normal. The patient was discharged with follow-up appointments. After 1 month, all tests were detected in the normal range (Laboratory findings of the patient are given in Table 1).

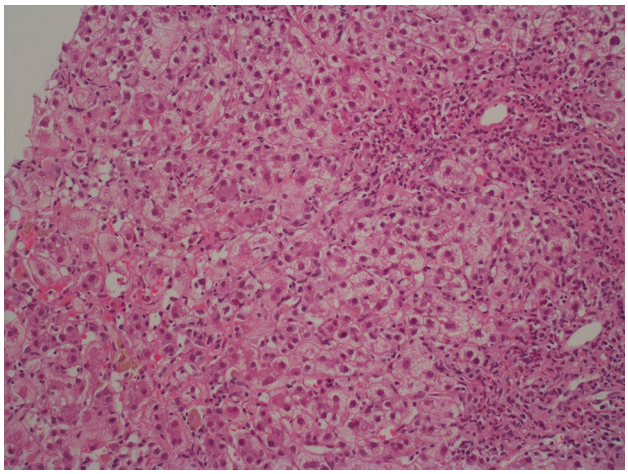

Fig. 1 Hepatocellular swelling, ballooning degeneration, cholestasis, and portal inflammation (7080/18: H&E×20)

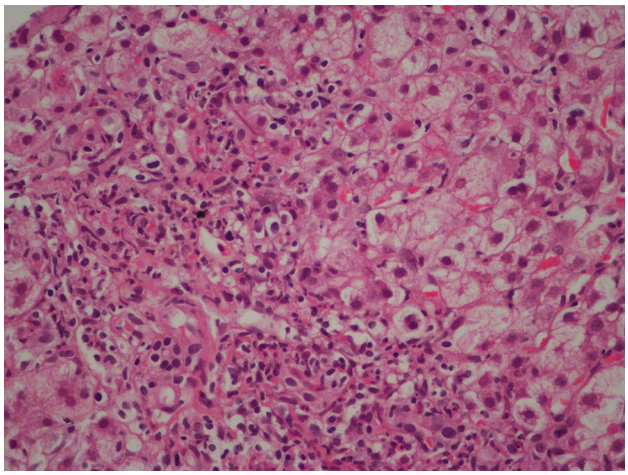

Fig. 2 Portal inflammation composed primarily of lymphocytes and a considerable number of neutrophils and piecemeal necrosis (7080/18: H&E×40)

Search strategy

To find the other similar cases in the literature we searched PubMed and Google Scholar using key words of "Cyclophosphamide induced hepatitis" or "Cyclophosphamide induced hepatotoxicity" up to 30 September 2018. After exclusion of 30 articles about experimental cyclophosphamide-induced hepatotoxicity studies performed on animals and 10 articles about cyclophosphamide-induced hepatotoxicity developed due to non-rheumatological diseases such as solid organ malignancy or hematological malignancy, we identified 8 articles about clinically proven hepatotoxicity secondary to CYC in the course of a rheumatologic disease [4–11].

Discussion

Drug-induced liver injury might be manifested as a clinical presentation ranging from asymptomatic liver test abnormalities to mild symptoms (nausea, loss of appetite, abdominal discomfort) to severe cytolytic or cholestatic jaundice, severe acute hepatitis and multi-organ insufficiency [1, 12]. CYC is frequently employed because of its immunosuppressive effect in spite of its well-established side effects, primarily, bone marrow suppression and gonadal toxicity. CYC-associated hepatotoxicity could be expected subsequent to high-doses, particularly in oncology patients and hematological patient group who had undergone bone marrow transplantation. At doses prescribed for rheumatological purposes, on the other hand, hepatotoxicity or acute hepatitis is typically not anticipated. However, CYC-induced liver toxicity, albeit rare, has been reported in the literature [4–11]. In our literature search, we have encountered with eight cases related to CYC-associated hepatotoxicity/hepatitis (ours being case nine). Out of nine cases, three had SLE, three had systemic vasculitis, one had rheumatoid arthritis, 1 had Sjogren's syndrome, and one had scleroderma. Acute hepatitis occurred after the initial administration in five patients, while two patients had symptomatic and other two had asymptomatic hepatotoxicity. Similar to our case, two of the previous cases had initially suffered hepatotoxicity after the first dose, followed by acute hepatitis which has emerged after the re-challenge with the second dose. Hepatotoxicity developed in one of the eight cases took place after each of three doses. It has taken 35 days to 24 months from oral intake to develop hepatitis or hepatotoxicity in the other 5 cases [4–11]. Provided that the medication is discontinued earlier, prognosis of drug-induced liver injury is usually good. On contrary, particularly when presented as acute liver injury, irreversible fulminant hepatic failure may emerge resulting in a high rate of mortality [1]. According to the reported outcomes, 1 patient had required liver transplantation due to acute hepatitis, 1 patient died, and all other patients recovered, including ours. The patient who had reacted to the drug in 3 h after intake, that is the earliest time course for manifestation of CYC side effects, passed away. Polypharmacy may sometimes pose a difficulty to distinguish which drug is the cause of hepatotoxicity. In a SLE case reported by Bacon et al., CYC usage was concomitant to acetylsalicylic acid (ASA), 6 weeks after which acute hepatitis has developed. Subsequent to the re-initiation in oral form, 6 months later, hepatotoxicity occurred [4]. While treating a microscopic polyangiitis (MPA) patient, Subranimam at al. infused IV 200 mg as an initial dose, repeated at the same dose 3 h and 2 weeks

Table 1 Laboratory findings before and after CYC treatment of our patient

	When SLE was diagnosed	The first time she applied to our center (1.5 months after CYC tablet was started)	On the day when CYC oral treatment was stopped	4 days after when CYC oral treatment was discontinued	10 days after when CYC oral treatment was discontinued	20 days after when CYC oral treatment was discontinued/ (Just before CYC IV)	10 days after CYC IV was given (admission to the external center)	20 days after CYC IV was given (admission to our center)	Maximum and lowest pathological values of the patient's test results	40 days after CYC IV was given	70 days after CYC IV was given
Date	31 January 2018	26 March 2018	27 March 2018	31 March 2018	6 April 2018	20 April 2018	3 May 2018	10 May 2018	–	31 May 2018	30 June 2018
Hb, g/dL	9.3	12.2	–	–	–	–	–	13.6	11.1	12.2	12.3
WBC, mm^3	2500	4900	–	–	–	–	–	3700	3700	5500	7000
PLT, mm^3	65.000	219.000	–	–	–	–	–	96.000	80.000	192.00	108.000
ESR, mm/h	78	9	–	–	—	22	21	19	–	19	53
CRP, mg/L	0.2	0.37	–	–	–	0.987	–	4.9	–	0.710	0.530
AST, U/L	23	47	76	151	105	25	692	1379	1379	69	18
ALT, U/L	25	98	128	363	326	28	579	1491	1491	93	18
LDH, U/L	311	419	413	433	469	–	572	652	652	232	306
ALP, U/L	38	43	36	41	55	–	126	162	170	118	49
GGT, U/L	–	24	21	88	88	–	229	231	418	279	36
T.bil, mg/dL	0.458	0.33	–	0.38	0.33	–	1.071	3.76	9.05	2.32	0.56
D.bil, mg/dL	0.127	0.15	–	0.16	0.11	–	0.699	3.38	8.07	1.83	0.37
Total protein, g/dL	6.61	7.32	–	6.28	–	–	–	6.82	6.28	6.68	7.35
Alb,mg/dL	4	4.7	–	3.9	3.9	–	4.2	4.3	3.9	4.6	5
PT, s	14.2	11.332	–	–	–	–	14.1	13.203	15.025	9.997	10.223
INR	0.89	0.975	–	–	–	–	0.96	1.2	1.386	0.881	0.904
PTT, s	24	25.783	–	–	–	–		34.120	38.432	30.221	28.853
Fibrinogen, mg/dL	270	213.437	–	–	–	–		291	173	366.345	–
Urinalysis											
Urobilinogen/bilirubin	Normal/negative	Normal/negative	–	–	–	–	–	+1/+2	+1/+4	+1/+4	Normal/negative
Medication	MP 1000 mg/day/3 days PPI (Lansaprasol) Ca+D vitamin	MP 32 mg/day CYC 100 mg/day PPI Ca+D vitamin	MP 32 mg/day	MP 32 mg/day	MP 32 mg/day	MP 32 mg/day	MP 8 mg/day	MP 8 mg/day	MP 60 mg/day UDCA NAC	MP 48 mg/day UDCA	MP 16 mg/day UDCA

SLE systemic lupus erythematosus, *Hb* hemoglobin, *WBC* white blood cell, *PLT* platelet, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *GGT* gamma glutamyl transferase, *T.bil* total bilirubin, *D-bil* direct bilirubin, *Alb* albumin, *PT* prothrombin time, *PTT* partial thromboplastin time, *CYC* cyclophosphamide, *MP* methyl prednisolone, *PPI* proton pump inhibitor, *Ca* calcium, *UDCA* ursodeoxycholic acid, *NAC* *n*-acetyl cysteine, IV; intravenous

later and detected patient had acute hepatitis [5]. ASA, prescribed for the case reported by Bacon et al., and both antituberculosis and antifungal agents used by the latter case bear the risk of hepatotoxicity. However, in repeated administrations CYC was given as a monotherapy which increases the likelihood that the following hepatotoxicity was caused by CYC [4]. In our patient, after the initial use of CYC, which was through oral route, asymptomatic liver enzyme elevation was detected. The patient was also using steroid, proton pump inhibitor, calcium and vitamin D, but no other drugs. Considering the SLE background of the patient, and as hepatotoxicity is not listed among the conventional side effects of CYC, although scarcely reported, liver enzyme abnormalities at the early phase were attributed to the disease (autoimmune hepatitis?). Therefore, IV CYC was delivered for neuro-lupus, 20 days after which acute hepatitis was determined. After the second use of CYC (IV), on the other hand, apart from steroid and CYC, the patient was free of accompanying medications and any other infectious causes, her serology results were negative for autoimmune hepatitis, and biopsy findings, similarly, were not supporting autoimmune hepatitis, but indeed were consistent with toxic hepatitis. When re-analyzed retrospectively, elevated LFT results which had been determined 6 weeks after the oral use of CYC at the initial period was also attributed to CYC as there was no concurrent medication other than steroid. Our patient's total score according to Naranjo adverse drug reaction (ADR) probability scale (score: 11) stands for definite ADR [13]. Based on the aforementioned data and evidence, we suggest our patient has experienced CYC-associated severe acute hepatitis. In the case reports of Bacon et al. and Subranimam et al., similar to our case, hepatitis took place after the second CYC administration [4, 5]. On the other hand, Martinez-Gabarron et al. reported a case who was given a first dose of CYC (500 mg) and experienced acute cholestatic hepatitis, after recovery of which the infusion of the second dose IV CYC (750 mg) was applied leading to acute hepatitis and eventually a third dose was given (oral CYC) followed again by acute hepatitis and then death [6]. Acute hepatitis and/or asymptomatic hepatotoxicity reported by Mok et al. and other 4 similar cases (case 6, 7, 8, and 9) developed 35 days to 24 months after the first (oral) ingestion of CYC. Mok et al. blamed the cumulative dose of the drug as the reason [7]. Cleland et al. argued SLE patients were susceptible to CYC hepatotoxicity [8]. In the entire patient group, however, only 3 out of 9 patients were inflicted by SLE. Therefore, judgment of increased susceptibility due to an underlying disease cannot be drawn readily.

What is the reason behind CYC-associated hepatotoxicity or acute hepatitis? Is it possible to predict?

Drug-induced hepatotoxicity may take the forms of idiosyncratic, autoimmune or toxic hepatitis. Resulting injury afterwards may arise in hepatocellular, cholestatic, or mixed type [1]. Differentiation between autoimmune and toxic hepatitis becomes challenging in those with an underlying autoimmune disease such as SLE or Sjogren's syndrome. Moreover, the likelihood that autoimmune hepatitis might be drug-associated makes the differential diagnosis even harder. Although liver biopsy does not always help with the differential diagnosis, still it should be performed in eligible patients for diagnostic or differential purposes. Only in 1 of the previous cases and in our case liver biopsy was carried out [7]. In both patients, biopsy findings provided evidence of drug-induced hepatitis (Clinical and laboratory findings and outcomes of nine patients including ours who had developed CYC-associated hepatotoxicity/hepatitis are given in detail in Tables 2, 3). It is not yet well elaborated why hepatotoxicity develops while on CYC in certain patients. Mechanism of CYC-induced hepatitis is, likewise, not clearly understood. It is rather not possible to anticipate either of these conditions. CYC-induced hepatotoxicity may idiosyncratically emerge in some genetically predisposed individuals. Although a rare occasion, its recognition is still of importance because of potentially serious results, despite the lack of methods to definitely diagnose and prevent. Diagnosis is based on clinical suspicion. Use of multiple drugs in combination may exert a challenge for its recognition. There is no specific treatment to reverse the liver injury caused by idiosyncratic hepatotoxicity. Early diagnosis and prompt withdrawal of the medication are, therefore, critical stages [12]. Idiosyncratic nature might be claimed for the first 4 patients as the side effect appeared after a short while of their initial doses. Earliest side effect was reported to arise 3 h after CYC administration (case 3) [5]. It has been speculated the genetic polymorphisms in some hepatic enzymes (cytochrome P450, glutathione *S*-transferase, and aldehyde dehydrogenases) which are engaged in CYC metabolism might be related with early onset [14]. In addition, an association has been found between hepatotoxicity and high doses of CYC and its toxic metabolites (acrolein and phosphor amide mustard) [15, 16]. Moreover, Gustaffson et al. reported inadequate debrisoquine hydroxylase activity inherited by patients with acute liver failure [9]. Similarly, while pointing out the likely role of pharmacogenetic variabilities in CYC metabolism, Synder et al. remarked that altered concentrations or activity of aldehyde dehydrogenase might be contributing to the liver injury, despite no enzyme level measurements having been implemented in the hepatocytes of patients with CYC-associated hepatotoxicity

Table 2 Clinical and laboratory findings of nine patients plus our case with CYC-induced hepatitis/hepatotoxicity in the literature

	Our case	Bacon et al. [4]	Subramaniam et al. [5]	Martinez-Gabarron et al. [6]	Mok et al. [7]	Gustafsson et al. [9]	Snyder et al. [10]	Clelelland et al. [8]	Akay et al. [11]
Age, years	19	23	48	57	67	58	67	36	40
Gender	Female	Female	Male	Male	Male	Female	Female	Female	Male
Rheumatological disease	SLE + pancytopenia + neurolupus	SLE + severe vasculitis	GPA + renal involvement	ANCA-associated vasculitis	Sjogren's syndrome + extraglandular involvement	RA	GPA	SLE + class 4 LN	Scleroderma
Medications for the diseases	CYC 100 mg/day oral MP 32 mg/day Ca + D vitamin PPI	CYC 1.5 mg/kg ASA 2.6–3.2 g Prednison 20 mg/day	Itrakanazol Anti-TBC therapy MP Plasmaferesis CYC 200 mg/IV	Pulse MP Plasmaferesis Hemodialysis CYC 500 mg/IV Ca + D vitamin PPI Sevelamer Furosemide	High dose steroid CYC 100 mg/day oral	Diclofenac CYC 2 × 50 mg/day/3 months After 3 months 2 × 100 mg/day	CYC 100 mg/day oral Prednison 20 mg/every other day	CYC 100 mg/day oral Prednison 10 mg/day Insulin Thyroxine	D-Penicillamine 1.5 years 2.5 years without medication Low-dose steroid CYC oral 100 mg/day
Symptoms and test results during the highest values of liver function tests	After 2 weeks, all drugs (except MP) were discontinued due to LFT elevation AST:47 ALT:98	After 6 weeks fever, nausea, vomiting, jaundice AST: about 3000 ALP: 200	Dyspnea, epigastric pain after 3 h ALT: 336 U/L (ALT: 568 after 4 days)	Sweating after 12 h, diffuse abdominal pain AST: 90 IU/L ALT: 76 IU/L Amylase: 173 IU/L	CYC oral 100 mg/day 6 months 50 mg/day 12 months 50 mg/ every other day (cumulative 40.5 g) Jaundice Alb: 28 g/dL AST: 408, ALT: 269 T.bil: 506 µmol/L Antismooth muscle antikoru pozitif	After a few days the dose was reduced to 2 × 50 mg/day due to nausea and vomiting Jaundice soon developed ASAT: 68 µkat/L ALAT: 40 µkat/L T.bil: 489 µmol/L PLT: 80×10^6 µ/L	Asymptomatic after 35 days ALT: about 700 Bil: normal	Jaundice after 10 weeks AST: 2265 U/L ALT: 2515 U/L Bil: 158 µmol/L INR: Normal Alb: 19 g/L	Because of progressive jaundice for 1 week, the patient was re-admitted after 45 days AST: 1806 IU/L ALT: 2407 IU/L D.bil: 6.3 mg/dL PT: 14.2
	Asymptomatic hepatotoxicity	Acute hepatitis	Symptomatic hepatotoxicity	Symptomatic hepatotoxicity	Acute hepatitis	Acute hepatitis + hepatic encephalopathy (acute liver failure)	Asymptomatic hepatotoxicity	Acute hepatitis	Acute hepatitis

SLE systemic lupus erythematosus, *GPA* granulomatosis with polyangiitis, *RA* rheumatoid arthritis, *ANCA* antineutrophilic cytoplasmic antibody, *LN* lupus nephritis, *ASA* acetyl salicylic acid, *anti-TBC* anti-tuberculosis, *PLT* platelet, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *T.bil* total bilirubin, *D-bil* direct bilirubin, *Alb* albumin, *PT* prothrombin time, *CYC* cyclophosphamide, *PPI* proton pump inhibitor, *Ca* calcium, *IV* intravenous, *MP* methyl prednisolone

Table 3 Outcomes of nine patients plus our case with CYC-induced hepatitis/hepatotoxicity in the literature

	Our case	Bacon et al. [4]	Subramaniam et al. [5]	Martinez-Gabarron et al. [6]	Mok et al. [7]	Gustafsson et al. [9]	Snyder et al. [10]	Cleleland et al. [8]	Akay et al. [11]
Rheumatological disease	SLE + pancytopenia + neurolupus	SLE + severe vasculitis	GPA + renal involvement	ANCA-associated vasculitis	Sjogren's syndrome + extraglandular involvement	RA	GPA	SLE + class 4 LN	Scleroderma
Recovery time in liver function tests	Improvement after 20 days after treatment with CYC, PPI and Ca + D vitamins was discontinued	Recovery after ASA and CYC discontinued	ALT enzyme was reduced to 104 after 2 weeks after all medications were discontinued	Improvement in following days	Improvement after 6 weeks of CYC discontinued	Since there was no improvement, liver transplant was done 4 days later	Improvement after 5 weeks of CYC discontinued	Improvement after 4 weeks of CYC discontinued	Improvement after 11 weeks of CYC discontinued
Second CYC administration and outcome	After 20 days, CYC IV 1 g was given Referral with jaundice, abdominal pain after 20 days AST:1379 ALT:1491 T.bil:3.76 D.bil:3.38 INR:1.3 Severe acute hepatitis	CYC started 50 mg/day due to cutaneous vasculitis developing after steroid treatment 6 months later Elevation of LFT after 2 weeks ALT: Approximately 500 Height of asymptomatic LFT	After 2 weeks CYC 200 mg/IV was given After 1 day, the same symptoms appeared and ALT: 1253 U/L Coagulopathy was detected Severe acute hepatitis	After 15 days CYC 750 mg/IV was given Right hypochondrium pain after 24 h AST:144 ALT:358 IU/L T.Bil:6.44 mg/dL Acute hepatitis improvement in following days After 15 days CYC was given 3 times (50 mg/day) Right hypochondrium pain after 4 days AST:271 ALT:281 Bil:0.74 mg CYC discontinued	–	–	–	–	–

Table 3 (continued)

	Our case	Bacon et al. [4]	Subramaniam et al. [5]	Martinez-Gabarron et al. [6]	Mok et al. [7]	Gustafsson et al. [9]	Snyder et al. [10]	Cleleland et al. [8]	Akay et al. [11]
Liver biopsy results	Hydropic changes in hepatocytes, balloon degeneration, cholestasis findings, marked neutrophil infiltration in the lobules, portal venous occlusive eosinophil and piecemeal necrosis in some portal areas	Without liver biopsy	Unable due to coagulopathy	Without liver biopsy	A grossly distorted hepatic acinar architecture with many hepatocytes exhibiting marked balloon degeneration, loss of hepatocytes in zone, moderate cytoplasmic and canalicular cholestasis, and infiltration of the portal tracts with a mixed acute and chronic inflammatory cells	Without liver biopsy	Without liver biopsy	Without liver biopsy	Without liver biopsy
Treatment	MP NAC ve UDCA	AZA	–	MMF	–	Liver transplanted	–	–	–
Outcome	Improvement	Improvement	Died of pneumonia and acute coronary event	Improvement	Improvement	Improvement	Improvement	Improvement	Improvement
Comment	Hepatotoxicity after first dose (100 mg/day oral) Acute hepatitis after 2nd CYC dose (IV 1 g) (idiosyncratic and challenge dose-dependent)	Acute hepatitis after first dose CYC (100 mg/day oral) Hepatotoxicity after the second CYC (50 mg/day) (idiosyncratic and challenge)	Hepatotoxicity after first dose CYC (IV) Acute hepatitis after 2nd dose CYC (IV) (idiosyncratic and challenge)	Hepatotoxicity after first dose CYC (500 mg/IV) Acute hepatitis after the 2nd CYC (750 mg/IV) Hepatotoxicity after 3rd dose CYC (oral) (idiosyncratic and challenge)	Cumulative dose effect (dose-dependent)	Cumulative dose effect (dose-dependent)	Cumulative dose effect (dose-dependent)	Cumulative dose effect (dose-dependent)	Cumulative dose effect (dose-dependent)

ASA acetyl salicylic acid, *LFT* liver function tests, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *T.bil* total bilirubin, *D-bil* direct bilirubin, *CYC* cyclophosphamide, *PPI* proton pump inhibitor, *Ca* calcium, *UDKA* ursodeoxycholic acid, *NAC n*-acetyl cysteine, *IV* intravenous, *MP* methyl prednisolone, *AZA* azathioprine, *MMF* mycophenolate mofetil

[10]. In other words, hepatotoxicity occupies various mechanisms and factors which change from one patient to another. Risk factors for hepatotoxicity include drug classes, patient variability, drug metabolism, and drug combination. Nevertheless, although physicians pay attention to avoid a risky combination, liver injury could not be predicted in most of the cases owing to the complicated drug metabolism and the effect of genetic and environmental factors. Hence, it is not always possible to predict the toxicity risk of the drug in advance. As a consequence, defining rare drug reactions and side effects is critical [1, 12].

In conclusion, to help building an increased awareness about such a serious side effect among the rheumatologists, we propose CYC should be listed besides the drugs such as MTX, leflunomide, sulfasalazine, and even azathioprine which are possible causes of hepatotoxicity in rheumatology practice. Furthermore, it should be kept in mind that this adverse effect may be manifested within hours after the first dose or subsequent to the repeated doses or even 2 years later through the increased cumulative dose.

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Compliance with ethical standards

Conflict of interest Author DUC, Author EÖ, Author EY and Author CK declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from our patient.

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