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Jaundice as a misadventure of a green tea (*camellia sinensis*) lover : a case report

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Abstract

The case of a 76-year-old retired surgeon and lover of green tea (*camellia sinensis*) infusions who developed a clinical, sero-biochemical and histological picture of severe subacute hepatitis is reported. The clinical presentation was that of jaundice with asthenia and weight loss. Abnormal liver function tests were associated with hyper-gammaglobulinemia, and the transient presence of anti-smooth-muscle antibodies and ANCA. Liver histology showed mixed features of lobular hepatitis with central collapses, portal inflammatory cells infiltration and interface hepatitis. All other potential causes of hepatitis were excluded on the basis of clinical, biochemical and serological data. Herbal preparation withdrawal resulted in a slow and continuous improvement with a complete clinical and sero-biochemical resolution after 7 months. (Acta gastroenterol. belg., **2008**, 71, **000-000**).

Key words : Green tea, *camellia sinensis*, infusions, hepatotoxicity, auto-immune hepatitis.

Introduction

Green tea (*Camellia sinensis*), used worldwide as a beverage or under the form of extract as a herbal medicine, was considered safe until recent years. Since 1999 micronized powder or extracts, especially the alcoholic one, have been recognized as potentially hepatotoxic and a number of preparations have been withdrawn from the market due to this potential side-effect (1-5). Furthermore, recent reports of liver toxicity of green tea infusions also appeared in the literature, the imputability of the herbal preparations having even been ascertained by positive rechallenge in some reported cases (6).

We report the case of a patient who presented with jaundice as well as with bio-serological and histological features of severe auto-immune hepatitis of seven months duration after drinking 6 to 7 bowls of green tea infusions of various origins per day.

Case report

A 76-year-old retired surgeon was admitted on May 2d, 2006 because of jaundice of one month duration, preceded by asthenia and weight loss of 16 kg within one month. There was no fever or abdominal pain.

His previous medical history included a slight but stable renal insufficiency, high blood pressure treated with ramipril (10 mg per day), and hypercholesterolemia treated by atorvastatine (10 mg per day), both medications taken since two years without any side effect. For years, he was also treated for restless leggs by clonazepam (0.7 mg per day), acetyl salicylic acid (160 mg per day) and by a small dose of dehydroepiandrosterone.

His alcohol consumption was only occasional. For years he has been a lover of green tea being used to drink 6-7 cups of *camellia sinensis* infusion per day. He was also used to taste various blends of tea, the main varieties which had been taken during the weeks preceding admission included 2 Japanese varieties (Sencha Fuji and Gyokuro) and one Chinese one (Lung Chin Imperial).

Physical examination at admission was normal except for the presence of deep icterus. Blood formula included : haemoglobin 13.4 g/dL (N : 12-17), white blood cell count $10.58 \times 10 \times 3/$ L, platelets $236 \times 10 \times 3/$ L. Creatinin was at 1.8 mg/dL [N < 1.4]), INR was 1.26 (N < 1.3). AST : 1044 IU/L (N < 33), ALT : 646 IU/L (N < 63), alkaline phosphatase : 331 IU/L (N < 94), gamma GT : 580 IU/L (N < 50), total bilirubin : 16.7 mg/dL (N < 1.2), direct bilirubin : 9.8 mg/dL (N < 0.7) and lactate dehydrogenase : 293 IU/L (N < 192). Iterative biochemical work-ups performed on an annual basis during the last years had always been reported unremarkably except for a slight and stable renal insufficiency.

Serological work-up showed post-vaccinal imunisation for both HAV and HBV and was negative for anti HCV and anti HEV. Serology for CMV, EBV and HSV did not show any sign of recent infection. Anti LKM, anti-nuclear and antimitochondrial antibodies were also negative, while anti-smooth muscle antibodies and ANCA were positive (1/80 and 1/160, respectively).

Abdominal ultrasound showed an hyperechogenic appearance of the periportal areas while magnetic resonance imaging showed hyperintense T2 and hypointense T1 image in the periportal areas.

A liver biopsy was performed which showed a picture of lobular hepatitis with acidophilic bodies and centrilobular collapses. Portal triads were diffusely enlarged with features of interface hepatitis. They showed a dense lymphoplasmocytic infiltration with a few eosinophils (Fig. 1 and 2).

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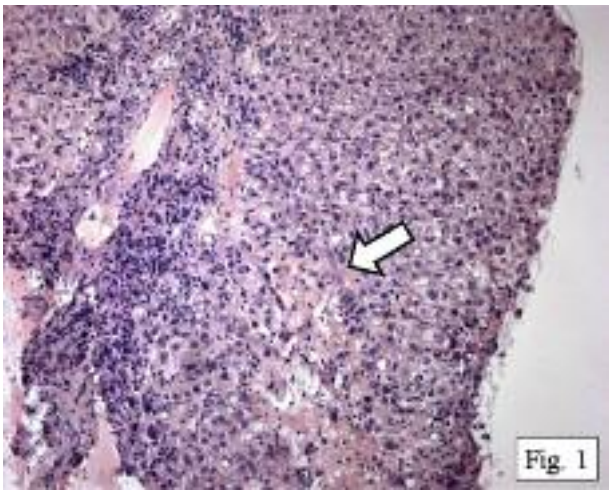

Fig. 1. — Hematoxylin and eosin staining, magnification 10×. Liver biopsy showing a large area of centrilobular collapse (arrow) together with an enlarged and infiltrated portal tract with interface hepatitis.

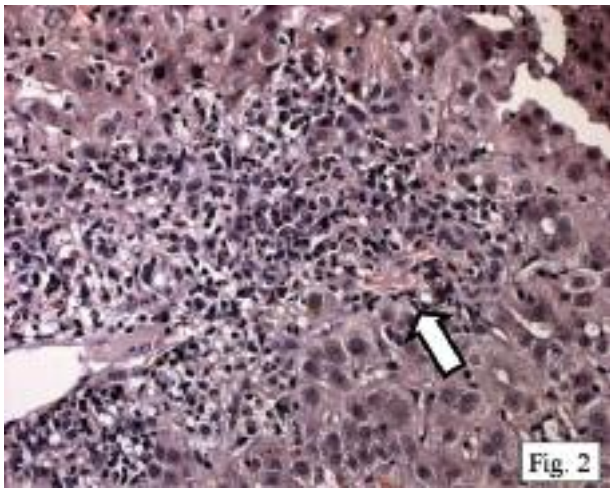

Fig. 2. — Hematoxylin and eosin staining, magnification 20×. Portal triad showing its infiltration by a dense mononuclear and eosinophilic infiltrate. Interface hepatitis is clearly seen (arrow).

Table I. — **Evolution of laboratory values in the reported case**

Laboratory values	Normal values	Admission	Day 28	Week 10	Week 19
INR	< 1.3	1.26		1.21	1.18
AST (IU/L)	< 33	1044	126	46	42
ALT (IU/L)	< 63	646	125	36	37
Alkaline phosphatase (IU/L)	< 94	331	118	51	33
Gamma GT (IU/L)	< 50	580	160	60	22
Total bilirubin (mg/dL)	< 1.2	16.7	4.2	0.9	0.7
Direct bilirubin (mg/dL)	< 0.7	9.8	2.0	0.3	0.2
Lactate dehydrogenase (IU/L)	< 192	293			

A presumptive diagnosis of subacute hepatitis of toxic origin was made.

The patient was advised to discontinue drinking green tea ; atorvastatine, clonazepam and dehydroepiandrosterone having been discontinued at admission.

Signs of clinical and biochemical improvement occurred as soon as five days after withdrawal, liver tests returning to normal values after four months, as did results of autoimmune testing (Table I). The total weight gain reached 20 kg. There has been no sign of relapse during 25 months of follow-up.

A lymphocyte transformation test in the presence of various dilutions of green tea up to 1/100 did not show any significant difference from control testing.

Discussion

We have reported the case of an elderly patient, green tea lover, treated for years by ramipril and atorvastatine without any apparent side effect and who developed a clinical and biochemical picture of severe subacute hepatitis. Histology and serological features were transiently suggestive of an auto-immune origin while green tea infusion withdrawal resulted in a complete disappearance of the clinical, biochemical and serological features within 7 months.

The diagnosis of *camellia sinensis*-induced hepatitis appears likely since the search for another origin remained negative and also since green tea withdrawal resulted in the resolution of disease. A diagnosis of type I auto-immune hepatitis occurring in a 76 year-old man is extremely unlikely as well as its spontaneous recovery without relapse during the following 22 months. Changes in the varieties of tea blends used by the patient and the amount of intake are also indirect arguments in favour of a causal relationship between green tea consumption and hepatitis. The role of a potential interaction between *camellia sinensis* and the other medications taken by the patient is also unlikely since studies have shown that green tea is unlikely to result in clinically significant effects on the disposition of drugs metabolized by CYP 1 A2, CYP 2D6, CYP 2C9 and CYP 3A4 (7,8,9).

In our patient a possible interaction with atorvastatin, metabolized by CYP3A4, can as such not be excluded but is unlikely because of the minor inhibitory effect of green tea on CYP3A4 and smaller daily amount of green tea taken. Moreover, hepatotoxicity related to atorvastatine seems to be an immuno-allergic reaction rather than a dose-dependent phenomenon (10).

We applicated the RUCAM score (11) to features observed in this case as this is the best validated method

Table II. — **Literature review of case reports of hepatotoxicity associated with the use of green tea infusions**

Article	Gender Age	Product	Onset	Clin. features	Biochemistry	Evolution	Reexposure
Jimenez-Saenz *et al.* 2006 (6)	♂, 45	green tea infusion, 6 cups/d	4 months	jaundice, asthenia	ALT : 1033, GPT : 1613, GGT : 394, AP : 310	normalisation in 2 months	elevation of liver tests with normalisation 2 months after cessation
Frederico *et al.* 2007 (13)	♀, 51	green tea infusions	5 years	history of elevated liver tests	AST-ALT : 4-5 ×, GGT : 200, AP : 200	normalisation after 2 months	
	♀, 20	green tea infusions	unknown	asymptomatic	ALT : 60, GGT 70, AP : 250	normalisation after 2 months.	

for causality assessment in acute hepatotoxicity. It was calculated at 7, which classifies causal relationship between the intake of green tea and the liver injury as probable.

Green tea is the non-fermented, non-oxidized product of leaves of *Camellia sinensis*.

It has been used since 5000 years as beverage and medicinal plant in China and India. In more recent years it has also been used in western countries under the form of extract or powder due to its antioxidant and anti-carcinogenic properties as well as for its weight loss properties.

Its main components are polyphenols (flavonoids, catechins), caffein, pectin, proteins and several minerals (12). The main catechins contained in green tea are epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG), the last one being present at the highest concentration. Because of minimal oxidation in the producing process of green tea, up to 30% of the dry weight of green tea consists of catechins, this in contrast with black tea, where the catechins become oxidized. These catechins are thought to be responsible for the antioxydant and anticarcinogenic effects of green tea. Recommended doses of extract preparations generally provide 125 to 250 mg of catechins per day. The levels of catechins in green tea infusions are estimated at : EGCG 117-442 mg/L, EGC 203-471 mg/L, ECG 16.9-150 mg/L, EC 25-81 mg/L and catechin 9.03-115 mg/L (12). However, the catechin content of various green tea blends varies considerably (12).

Reports of hepatotoxicity of green tea extracts were first published in 2001 (1-4) and the product Exolise® (a dried ethanolic extract of green tea) was withdrawn from the market due to the occurrence of cases of hepatotoxicity. Later, reports of hepatotoxicity on micronized powder of *Camellia sinensis* also appeared in the literature (5). Recently, reports of hepatotoxicity following the intake of green tea infusions were also published (6,13) (Table II).

The prevalence of such side effect is unknown. As observed in the majority of cases liver toxicity it is higher in females, symptoms ranging from asymptomatic elevation of liver enzymes to acute liver failure. Biochemical features are those of a mixed-type liver injury which occurs between weeks and months after the intake of green tea in the reported cases (1-6,14-16). Reported morphological changes include lobular necrosis under the form of centrilobular necrosis with or without bridging with mild lobular inflammation as well as portal inflammation and periportal piecemeal necrosis (14,16). Green tea withdrawal led to resolution in all cases, only one case having been transplanted for liver failure (1-6,14-16). Rechallenge in 3 cases led to the relapse of biochemical feature in all 3 cases (4,6,14), normalisation again occurring after cessation of intake of the herbal product.

The mechanism of hepatotoxicity is not known. However, phenolic acids and catechins were found to be cytotoxic towards isolated rat hepatocytes, evaluated by a trypan blue exclusion test (17). The major cytotoxic mechanisms found were mitochondrial membrane potential collapse and reactive oxygen species formation. In contrast, GSH conjugation, methylation and metabolism by NAD(P)H : quinone oxidoreductase are important in detoxifying gallic acid and EGCG. In vivo liver injury was evaluated by measuring the level of ALT 24 hours after intraperitoneal injection of a single dose of tea phenolic acids or catechins in mice (17). In all mice a dose-dependant significant increase in plasma ALT levels was seen with injection of gallic acid, propyl gallate, tannic acid and EGCG. ECGC even caused death in mice in less than 24 hours at a dose of 150 mg/kg. Other factors such as immuno-allergic mechanisms or a genetic predisposition might also play a role.

In conclusion, as for other herbal medicines, information about green tea consumption should be part of the interview of any patient presenting with liver enzyme abnormalities or hepatic failure.

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