Acute hepatitis after treatment for hair loss with oral green tea extracts (Camellia Sinensis)

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Abstract

Nutritional additives based on green tea have been claiming various beneficial health effects. However, several case reports on hepatotoxicity after the intake of green tea derivatives containing Camellia Sinensis have been published. We report a patient with an acute hepatitis after intake of an oral green tea derivative claiming protection against hair loss, showing a histological image compatible with drug induced hepatitis. Other important causes of hepatitis were excluded. After cessation of this nutritional additive there was a rapid and sustained recovery. We raise concern about the safety of nutritional additives with few proven beneficial effects and want to emphasize the importance of accurate and thorough history taking, with attention for over the counter drugs and herbal products. (Acta gastroenterol. belg., **2009**, 72, **262-264**).

Key words : green tea, camellia sinensis, acute hepatitis, liver failure, hepatotoxicity.

Introduction

Green tea and other herbal drugs have been promoted as food supplements claiming several beneficial health effects. However several case reports have been published showing hepatotoxicity after ingestion of green tea derivatives (1-5) and other herbal products (6). We report a case of a woman who developed an acute toxic hepatitis after the intake of a food supplement claiming protection against hair loss, which contains Camellia Sinensis. Until now, all case reports were in connection to nutritional supplements aiming at weight reduction.

Case report

A forty-one year old woman with an unremarkable medical history was referred to the outpatient clinic because of jaundice since a few days. There were no further complaints like concomitant nausea, vomiting, abdominal pain, fever, or weight loss. A further functional enquiry was negative. Family history was negative. Patient denied the use of alcohol or drugs. A careful history of drug use revealed that six months before admission she started taking Densitive® (Kerastase Nutritients, produced by L'Oréal), a natural product containing Camellia Sinensis (27%) claiming protection against hair loss. She used 2 tablets daily for the first three months, after which the dosage was lowered to 1 tablet a day. A dosage of 2 tablets corresponds with 140 mg of polyphenol monomers derived from Camellia Sinensis Kuntze extracts (27%).

The patient used low doses of paracetamol (less than 3 gram a day) less than once a week. She had not been travelling outside Europe for the last two years.

Clinical examination confirmed the jaundice. The body temperature was 36.2° C, blood pressure was 125/75 mmHg, pulse was 76/minute. Clinical examination of heart and lungs was unremarkable. Abdominal examination was painless, no masses were observed, bowel sounds were normal. There were no clinical signs of neurological dysfunction.

Laboratory investigation showed a total serum bilirubin of 13.6 mg/dL (normal range 0.2-1 mg/dL), with a direct fraction of 9.8 mg/dL (normal range 0-0.25 mg/dL). Aspartate aminotransferase was 1358 U/L (normal range 5-30 U/L), alanine aminotransferase 2801 U/L (normal range 5-36 U/L), gamma glutamyl transferase 322 U/L (normal range 5-36 U/L) and alkaline phosphatase 251 U/L (normal range 32-104 U/L). International normalized ratio of prothrombin time was 1.1 (normal range 0.8-1.2). Peripheral blood count, serum creatinine, amylase and lipase and electrolytes were within normal range. Autoimmune markers (antinuclear factor, anti smooth muscle antibody, anti mitochondrial antibody) proved negative, although immunoglobulin G was slightly increased. Immunoglobulin M was within normal range. Serum paracetamol level at admission was 1.4 µg/mL. Viral serology for hepatitis A, B and C, Epstein Barr virus, Cytomegalovirus and Herpes Zoster were all negative. Ultrasonography and computed tomography of the liver and the abdomen showed a global hypodens aspect of the liver, without enlargement of biliary ducts. Calculi were not observed.

Histological examination of a liver biopsy specimen was compatible with drug induced hepatitis. More in particular it showed an important inflammatory infiltration of the portal areas (Fig. 1) with granulocytes, eosinophils, lymphocytes and a few plasmocytes, moving to the liver parenchyma (Fig. 2), with a few necrotic hepatocytes

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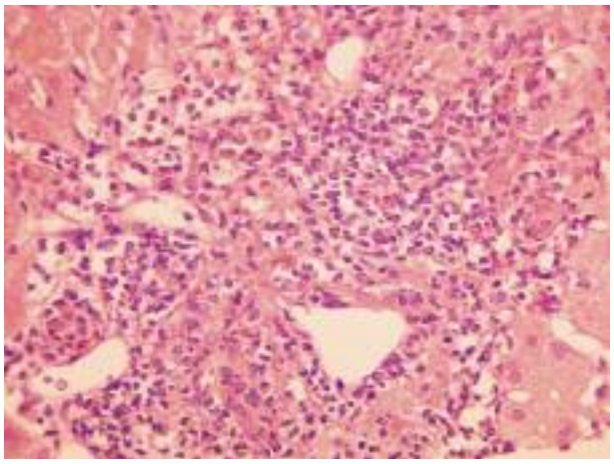

Fig. 1. — Hematoxylin and eosin stain, magnification 40×. Portal area with a multicellular infiltration, including eosinophils.

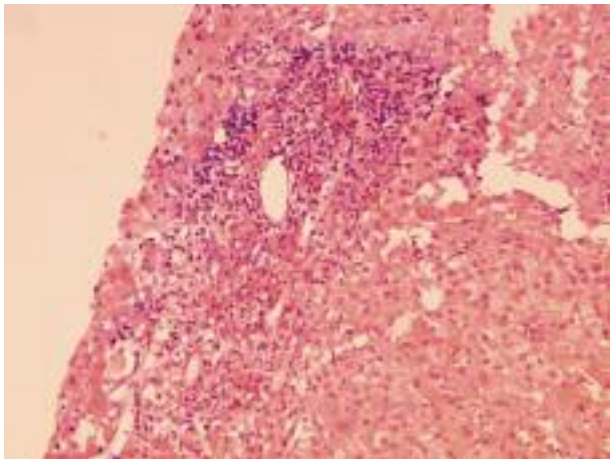

Fig. 2. — Hematoxylin and eosin stain, magnification 20×. Portal area with interface hepatitis. An inflammatory process is infiltrating the parenchyma.

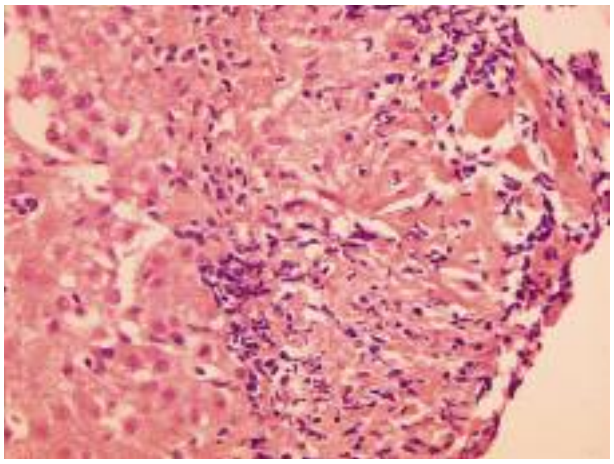

Fig. 3. — Hematoxylin and eosin stain, magnification 40×. Liver cell necrosis with different necrotic hepatocytes.

(Fig. 3). There was an important intrahepatic cholestasis. There were no signs of cirrhosis or iron overload.

After cessation of the intake of Densitive® the aspartate aminotransferase levels decreased from 1358 U/L to 1014 U/L and 902 U/L respectively within 48 hours en 5 days. Alanine aminotransferase decreased from 2801 U/L to 2142 U/L and to 1510 U/L after 48 hours and five days respectively. Total bilirubin level remained high. There was never any sign of liver failure. After one month, her jaundice had disappeared completely. Control of biochemistry showed a total bilirubin of 1.79 mg/dL, aspartate aminotransferase of 41 U/L and alanine aminotransferase of 107 U/L.

Discussion

Tea is one of the most consumed beverages in the world. It is prepared from the dried leaves of Camellia Sinensis, a member of the Theacea family. Beneficial effects like cancer protection and protection against atherosclerosis have been attributed to green tea (7). The report of these beneficial effects triggered the commercialisation of nutritional additives based on green tea claiming weight loss and protection against hair loss. However, several case reports suggest a causal relationship between oral intake of Camellia Sinensis extracts and hepatotoxicity (1-5). Indeed, a literature review of Sarma *et al.* (8) revealed 216 case reports of toxicity after intake of green tea products, including 34 reports concerning liver damage. Twenty-seven of those were categorized as possible causality and seven as a probable causality.

Moreover, Bonkovsky (9) reported a patient who developed an acute hepatitis after intake of green tea extracts with a rapid recovery upon discontinuation and a relapse after rechallenge.

In most of the reported patients there was a full recovery after the cessation of the intake. However, two case-reports were published of patients with acute liver failure leading to orthotopic liver transplantation (10, 11).

It is of course difficult to prove a causal relationship between the intake of the dietary supplement and the toxic hepatitis in our patient. However histopathologic examination of a liver specimen was compatible with toxic drug induced hepatitis and our patient showed no evidence of a viral or auto-immune hepatitis, hemochromatosis or ingestion of another hepatotoxic product. Furthermore, after cessation of the tablets, there was an important decrease of the transaminases within a few days.

After excluding other aetiologies, considering the outcome after stopping the product and the evidence of previous case-reports, we conclude that Densitive® was the causal agent of this acute hepatitis. As the literature mentions cases of liver transplantation because of liver failure a rechallenge was not considered.

There are relatively few worldwide observations of liver toxicity compared to the level of consumption of

green tea derivatives. In a recent prospective study of drug induced liver injury (DILI) in the United States published in Gastroenterology (12) DILI from any single medication was a rare clinical event occurring in less than 1 per 10,000 to 100,000 of subjects taking the drug. In a cohort of 300 patients the total number of cases of DILI due to dietary and herbal supplements was small (n = 28). Supplements containing green tea as a major ingredient caused at least 6 of the 28 cases. As with most DILI, the majority of patients with Camellia Sinensis related DILI have been women. In a letter to the editor (13), Bonkovsky stated that given the relative rarity of the reaction it seems likely that host genetic factors are important in modulating susceptibility. We are faced with a growing amount of drugs in which host genetic factors seem to play a major role explaining adverse drug reactions, for example the Abacavir story (14). This opens the era where a pharmacogenetic test can be used to prevent a specific toxic effect of a drug (15).

In the case of green tea the risk factors and the pathogenesis are poorly understood. Green tea is an abundant source of tea phenolics, hydroxylated aromatic organic substances. In tea these are mostly in the form of gallic acid and its catechin derivatives. Major green tea catechins are epigallocatechin-3-gallate (EGCG), pigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) (16). Schmidt *et al.* (17) exposed rat hepatocytes in primary culture to various hydroalcoholic green tea extracts. Exposure to high levels of EGCG exerted acute toxicity in rat liver cells in vitro. O'Brien (16) confirmed the major role of EGCG in hepatotoxicity, as well in mice hepatocytes as in mice in vivo. Mechanisms for hepatic damage involved mitochondrial toxicity and formation of reactive oxygen species (including hydrogen peroxide).

In conclusion we have good reasons to believe that the hepatotoxicity in our patient was caused by intake of green tea derivatives claiming protection against hair loss. Though our patient recovered totally, serious cases were reported necessitating liver transplantation. For this reason we want to express our concern about the use of nutritional additives proving only dubious beneficial effects but against whom evidence of serious side effects is growing rapidly. We also want to emphasize the importance of a careful history taking in probable cases of liver toxicity, including the active questioning for over the counter drugs and herbal products.

References

1. VIAL T., BERNARD G., LEWDEN B., DUMORTIER J., DESCOTES J. Acute hepatitis due to Exolises, a Camellia sinensis-derived drug. *Gastroenterol. Clin. Biol.*, 2003, **27** : 1166-1177.
2. THIOLET C., MENNECIER D., BREDIN C., MOULIN O., RIMLINGER H., NIZOU C. *et al.* Acute cytolysis induced by Chinese tea. *Gastroenterol. Clin. Biol.*, 2002, **26** : 939-940.
3. PEDROS C., CEREZA G., GARCIA N., LAPORTE J.R. Liver toxicity of Camellia sinensis dried ethanolic extract. Letter. *Med. Clin. Barc.*, 2003, **121** : 598-599.
4. GARCIA-MORAN S., SAEZ-ROYUELA F., GENTO E., LOPEZ MORANTE A., ARIAS L. Acute hepatitis associated with Camellia tea and Orthosiphon stamineus ingestion. Letter. *Gastroenterol. Hepatol.*, 2004, **27** : 559-560.
5. JIMENEZ-SAENZ M., MARTINEZ-SANCHEZ M.C. Acute hepatitis associated with ingestion of green tea infusions. *J. Hepatology*, 2006, **44** : 616-617.
6. HARDEMAN E., VAN OVERBEKE L., ILEGEMS S., FERRANTE M. Acute hepatitis induced by greater celandine (chelidonium majus). *Acta Gastroent. Belg.*, 2008, **71** : 281-282.
7. CABRERA C., ARTACHO R., GIMENEZ R. Beneficial effects of green tea. A Review. *J. Am. Coll. Nutr.*, 2006, **25** : 79-99.
8. SARMA D.N., BARRETT M.L., CHAVEZ M.L., GARDINER P., KO R., MAHADY G.B., MARLES R.J., PELLICORE L.S., GIANCASPRO G.I., LOW DOG T. Safety of green tea extracts : A systematic review by the US Pharmacopeia. *Drug Saf.*, 2008, **31** : 469-84.
9. BONKOVSKY H.L. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). *Ann. Intern. Med.*, 2006, **144** : 68-71.
10. GLORO R., HOURMAND-OLLIVIER I., MOSQUET B., MOSQUET L., ROUSSELOT P., SALAMÉ E., PIQUET M.A., DAO T. Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea. *Gastroenterol. Hepatol.*, 2005, **17** : 1135-1137.
11. MOLINARI M., WATT K.D.S., KRUSZYNA T., NELSON R., WALSH M., HUANG W-Y. *et al.* Acute liver failure induced by green tea extracts : case report and review of the literature. *Liver Transpl.*, 2006, **12** : 1892-1895.
12. CHALSANI N., FONTANA R., BONKOVSKY H., WATKINS P., DAVERN T., SERRANO J., YANG H., ROCHON J. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the united states. *Gastroenterology*, 2008, **135** : 1924-34.
13. JAVAID A., BONKOVSKY H. Hepatotoxicity due to extracts of Chinese green tea (Camellia Sinensis) : A growing concern. *J. Hepatol.*, 2006, **45** : 334-5.
14. MALLAL S., NOLAN D., WITT C. *et al.* Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*, 2002, **359** : 727-32.
15. MALLAL S., PHILLIPS E., CAROSI G. *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *N. Engl. J. Med.*, 2008, **358** : 568-79.
16. GALATI G., LIN A., SULTAN A.M., O'BRIEN P.J. Cellular and in vivo hepatotoxicity caused by green tea phenolic acids and catechins. *Free radical Biology and Medecine*, 2006, **40** : 570-80.
17. SCHMIDT M., SCHMITZ HJ., BAUMGART A., GUÉDON D., NETSCH M.I., KREUTER MH., SCHMIDLIN CB., SCHRENK D. Toxicity of green tea extracts and their constituent in rat hepatocytes in primary culture. *Food and Chemical Toxicity*, 2005, **43** : 307-14.