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Concentrated green tea extract induces severe acute hepatitis in a 63-year-old woman – A case report with pharmaceutical analysis

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ABSTRACT

Etnopharmacological Relevance: The popularity of concentrated green tea extracts as dietary supplements for a wide range of applications is increasing due to their health-promoting effects attributed to the high amounts of catechins they contain. The most important of the green tea catechins is (−)-epigallocatechin-3-O-gallate (EGCG). While their beneficiary effects have been studied extensively, a small number of adverse events have been reported in the medical literature. Here we present a typical reversible course of severe hepatitis after green tea consumption.

Materials and methods: The case study describes in a 63-year old woman during treatment with green tea-capsules upon recommendation of a cancer support group.

Results: The histological finding was consistent with drug induced hepatitis, and other possible causes of hepatitis were excluded. According to the CIOMS/RUCAM score the causality was assessed as "probable". After discontinuation of medication, followed by extracorporal albumin dialysis, rapid and sustained recovery occurred. Pharmaceutically analysis (HPLC) of the green tea capsules did not give evidence for contaminants but revealed the two typical compounds of green tea, namely (−)-epigallocatechin-3-O-gallate (EGCG, 93.2%) and epicatechin (EC, 6.8%) at a very high dose level.

Conclusion: The present case highlights the fact that such concentrated herbal extracts from green tea may not be free of adverse effects under certain circumstances. There is still a lack of a uniform European Union-wide surveillance system for adverse drug reactions of herbal products. Therefore this case underlines the importance of public awareness in the potential risks in use of herbal products.

1. Introduction

Concentrated herbal extracts have become increasingly popular as nutritional supplements and are consumed with the intent to achieve primary, secondary or tertiary prevention of a wide range of chronic diseases and civilisatory illnesses (Chacko et al., 2010; Kim et al., 2014). Capsules of green tea extract made from dried, non-fermented leaves of the plant *Camellia sinensis* (L.) Kuntze (belonging to the *Theaceae* plant family) are widely consumed because of the beneficial health effects attributed mainly to its polyphenolic components. Among them are the antioxidative catechins, most notably the compound (−)-epigallocatechin-3-O-gallate (EGCG), its numerous oligo- and polymers and other substituted and non-substituted flavan-3-ols. EGCG amounts to more than 50% of the flavan-3-ol fraction in green tea extracts (Nagle et al., 2006; Quideau et al., 2011).

Typical green tea concentrates are prepared by aqueous extraction at temperatures of 80–100 °C depending on the desired polyphenol and catechin content (Khokhar and Magnusdottir, 2002; Graziose et al., 2010; Unachukwu et al., 2010). After removal of the solvent the resulting dry extract is filled into capsules at different dosages. Typically one capsule is administered once a day after a meal (Lambert et al., 2010). In Europe, herbal products are marketed by domestic or US and Asian manufacturers and are regulated including mandatory pre- and post-marketing surveillance (Mohamed and Frye, 2011; Stickel et al., 2011). Products imported directly from suppliers outside of Europe through online retailers may not always adhere to these strict standards and may therefore contain contaminations like heavy metals, pathogens or undeclared ingredients (Navarro, 2009), which may all contribute to hamper causality assessments in

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clinical cases of suspected herbal hepatotoxicity (Teschke et al., 2012a; Teschke et al., 2012b).

2. Case report and pharmaceutical analysis

On February 8, 2011, a 63 year old woman was admitted to our department with ≈40-fold elevated transaminases (alanine aminotransferase (ALT) 2101 U/l, aspartate aminotransferase (AST) 1779 U/l) and elevated cholestasis parameters (total bilirubin 14.4 mg/dl, alkaline phosphatase (AP) 209 U/l, gamma-glutamyltransferase (γGT) 150 U/l). International normalized ratio of prothrombin time was within normal range as well as laboratory values of renal function, electrolytes, lipase and complete blood count.

Five days before, the patient was admitted to a local hospital with lassitude, newly occurred painless jaundice, mild pruritus and discoloration of stool and urine. Clinical signs of bleeding, abdominal pain or swelling, fever, weight loss, sleeplessness and ingestion of exotic meals within the last months were negated. The patient's last travel outside Europe was a trip to the Dominican Republic five years ago. Allergy, contact with solvents and abuse of alcohol were also denied.

2.1. Medical history

Non-metastasized sinistral breast cancer receiving breast conserving surgery followed by radiotherapy in 2000, locoregional recurrence in 09/2006 and retreatment with resection, radiation therapy and adjuvant treatment with anastrozole (non-steroidal aromatase inhibitor); stabilization surgery of osteoporotic lumbar vertebral fracture in 2004, cholecystectomy and hysterectomy for uterine prolapse in 1980 and arterial hypertension. Concurrent oral medication (discontinued 4 days before admitting to our department) included anastrozole 1 mg (since 2006), ramipril 2.5 mg (since 2008), oxybutynine 5 mg (since 15 years), vitamin D3-supplementation (since 02/2010), capsules with extracts from decaffeinated green tea (725 mg extract, 1 capsule/day since 12/21/2010). All drugs were taken in the morning, except green tea capsules which were ingested daily after lunch.

Symptoms were unlikely to be caused by cardiac deficiency as there was no previous history of cardiac disease, electrocardiogram and arterial blood pressure were normal. Physical examination showed no pathological findings except pronounced jaundice of sclerae and skin. Vital signs were within normal range, body temperature was 36.2 °C, and body weight was 72 kg. Ultrasound revealed a normal-sized liver without any signs of intra- or extrahepatic cholestasis, no intrahepatic tumor, no ascites, normal venous and arterial perfusion and a normal spleen and pancreas. Serological analyses were negative for hepatitis A, B, C, D, E, cytomegalovirus and Epstein–Barr virus. There was no serological evidence of autoimmune hepatitis or cholangitis (normal findings for antinuclear-, anti-smooth muscle, and anti-microsomal antibody). Furthermore there was no suggestion for storage diseases like hemochromatosis or Wilson disease in laboratory tests.

On the day after admission the patient underwent a percutaneous liver biopsy which showed patterns of an extensive florid hepatitis with predominantly centrolobular residuals of hepatocellular damage and active regeneration signs with activated macrophages and minor portal infiltration by inflammatory cells with single eosinophilic plates (Fig. 2). There were no signs of fibrosis, cirrhosis or hemosiderosis. In summary, the histological pattern was highly indicative of a toxic mechanism. An autoimmune cause has been considered alternatively, but serological findings were negative for the corresponding autoantibodies. The patient stayed hospitalized and was monitored for changes in clinical chemistry. All medications were immediately discontinued. One day after admission, transaminases reached peak values of GOT (2054 U/l), GPT (2204 U/l) (Fig. 1). Levels of bilirubin increased further. Quick and INR values were within normal range during the whole follow-up period. Because of an increase of bilirubin to a peak value of 20.4 mg/dl, persistent lassitude and pruritus the patient received albumin dialysis with the molecular adsorbent recirculating system (MARS®) on days 9 and 10 after admission. Subsequently the patient's general condition improved and at day of discharge (February 22, 2011) bilirubin was 9.5 mg/l, GOT 621 U/l, GPT 865 U/l, and γGT 152 U/l (Fig. 1). One week later there was an outpatient consultation at our department: liver values had decreased and general condition had

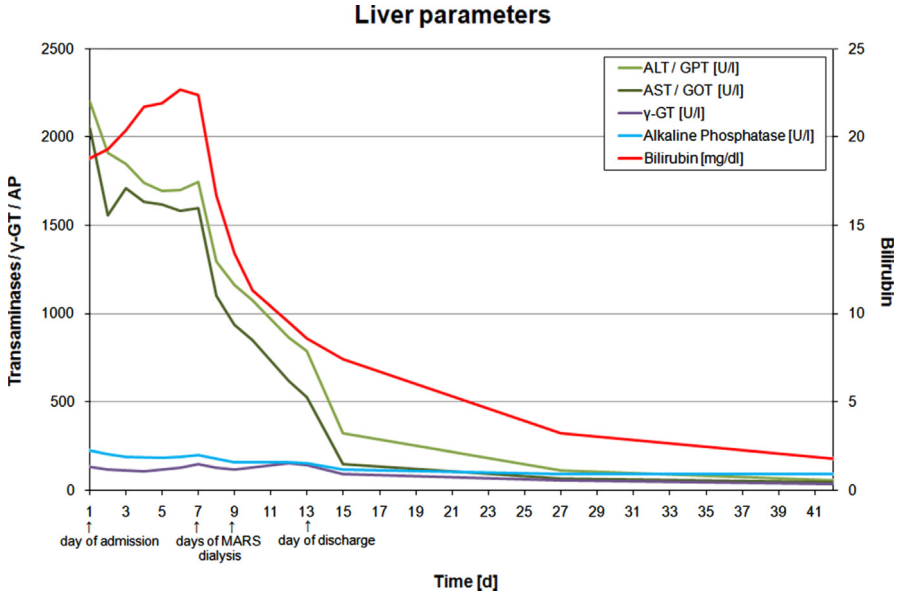

Fig. 1. History of liver parameters after admission to our department and in ambulatory consultation. The left *y*-axis shows the different liver enzymes activities in units per liter (ALT, alanine aminotransferase, syn. glutamate pyruvate transaminase; AST, aspartate aminotransferase, syn. glutamate oxaloacetate transaminase; γ-GT, γ-glutamyltransferase; AP, alkaline phosphatase). The right *y*-axis displays total bilirubin in milligrams per deciliter.