Clinical Case Report

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Reversible severe fatty liver induced by capecitabine

A case report

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Abstract

Rationale: Capecitabine (CAP) is a chemotherapeutic agent used to treat breast and gastrointestinal cancers. The most common adverse reactions of CAP primarily included gastrointestinal and dermatological effects. Whereas, the CAP-induced fatty liver had never been reported.

Patient concerns: In this study, a-69-year old female presented a history of hypertension with regulated blood pressure, whereas diabetes mellitus, hyperlipidemia, and hepatitis were excluded. No alcohol,tobacco, or other drugs use was declared.

Diagnoses: She was diagnosed as infiltrating ductal carcinoma of left breast with the hepatic and pulmonary metastasis. The dihydropyrimidine dehydrogenase (DPD) deficiency is not involved.

Interventions: She received treatment with CAP that was administered orally at a dosage of 1500mg twice daily intermittently (2weeks on/1 week off). The treatment was well-tolerated any typical adverse reactions such as diarrhea, nausea, and hand-foot syndrome (HFS) were noted. The parameters of the functional liver, the total cholesterol, and triglyceride were in normal ranges before and after therapy. After 3 cycles of the treatment, computed tomography (CT) scan revealed signs of fatty liver. After a 10-cycle course, CAP was substituted with tamoxifen because of the further aggravation of fatty liver.

Outcomes: Several months after withdrawal, the follow-up CT scans demonstrated significant improvement of fatty liver.

Lessons: We presented a case of breast cancer with severe fatty liver as a consequence of the administration of CAP that was not involved in DPD deficiency or CAP-associated hypertriglyceridemia; these potential adverse effects of therapy with CAP should be intensely investigated.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = including aspartate aminotransferase, CAP = capecitabine, DPD = The dihydropyrimidine dehydrogenase, GGT = gamma-glutamyltransferase, HFS = hand-foot syndrome, L/S ratio = liver-to-spleen CT ratio, TC = the total cholesterol, TG = triglyceride.

Keywords: breast, cancer, capecitabine, fatty liver, reversible

1. Introduction

As a new generation of orally administered fluoropyrimidines, capecitabine (CAP) was considered as the first-line therapy, alone or combined with other chemotherapeutics, for a majority of gastrointestinal tumors.[1] Thus, the necessity of a convenient therapy is fulfilled, providing an improved safety/tolerance profile.[2] Hence, the CAP therapy proved to be a safe and efficient treatment option for advanced breast cancer patients with excessive liver metastases.[3,4]

The dihydropyrimidine dehydrogenase (DPD) was a rate-limiting enzyme involved in the catabolism of 5-FU; thus, the deficiency of DPD induced the accumulation of 5-FU, thereby increasing the risk of toxic events.[5] The deficiency was an autosomal recessive metabolic disorder as a consequence of the allelic mutations within the *DPYD* gene.[6] Notably, the unanticipated, severe, as well as fatal toxicity linked to CAP had been described in patients with DPD deficiency.[7,8] Thus, in addition to severe kidney dysfunction, severe leukopenia, pregnancy, or lactation, DPD deficiency was also listed as a contraindication of CAP.[9]

Intermittent CAP, orally administered twice daily for 2 weeks followed by an interval of 1 week, was recommended due to basic systemic 5-FU levels and less toxicity. [10] The most common adverse reactions of CAP included gastrointestinal and dermatological effects, including diarrhea, nausea, vomiting, stomatitis, and hand-foot syndrome (HFS)[4]; hypertriglyceridemia was also observed as an uncommon side effect. However, the CAP-induced fatty liver has not yet been reported. Herein, we presented a case of the reversible severe fatty liver as a consequence of the administration of CAP that was not involved in DPD deficiency or CAP-associated hypertriglyceridemia, which might cause potentially severe toxicity warranting further attention.

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2. Case report

A 59-year-old patient diagnosed with infiltrating ductal carcinoma of left breast was admitted to our Department of Tumor Rehabilitation, First Hospital, Wenzhou Medical University, Ouhai, Wenzhou. The patient presented a history of hypertension with regulated blood pressure, whereas diabetes mellitus, hyperlipidemia, and hepatitis were excluded. No alcohol, tobacco, or other drugs use was declared. After a modified radical mastectomy in October 2010, the patient underwent 6 cycles chemotherapy with TEC regimen (paclitaxel + epirubicin + cyclophosphamide) followed by endocrine therapy with arimidex. Owing to the hepatic and pulmonary metastasis, the schedule was replaced by GP regimen (gemcitabine and cisplatin) for 6 cycles and endocrine intervention with exemestane in August 2013. However, the progression of the tumor after 6 months obligated us to convert to another treatment with CAP, which was administered orally at a dosage of 1500 mg twice daily, intermittently (2 weeks on/1 week off).

The treatment was well-tolerated without any typical adverse reactions such as diarrhea, nausea, and HFS. During the administration of CAP, the parameters of the functional liver, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT), were in normal ranges. Before and after therapy, the total cholesterol (TC) (range, from 2.44 to 5.17 mmol/L) and triglyceride (TG) (range, from 0.40 to 1.70 mmol/L) were 4.45, 1.06 and 3.79, 1.19 mmol/L, respectively, without any abnormality. After the third cycle of the treatment, the computed tomography (CT) scan of the abdomen revealed signs of fatty liver around hepatic portal, and the liver-to-spleen CT ratio (L/S ratio) was 0.74 (38.69/52.29) (Fig. 1B); the ratio was 1.16 (64.13/55.51) (Fig. 1A) upon the onset of CAP regimen. Simultaneously, the value of serum total bilirubin (TB) elevated from 16 to 24 μmol/L (normal range 3.4–17.1 μmol/L), subsequently, followed by a maximum of 40 μmol/L. The liver-protecting capsules were utilized with ursofalk to relieve the damage to the liver. However, the continued scan indicated the further aggravation of fatty liver with the L/S ratio of –0.13 (–7.24/54.16) (Fig. 1C); thus, CAP was substituted with tamoxifen in October 2014 after a 10-cycle course. Three months after withdrawal, the value of serum bilirubin declined to 11 μmol/L. The follow-up CT scans demonstrated that the L/S ratio returned to 0.15 (8.11/53.3)

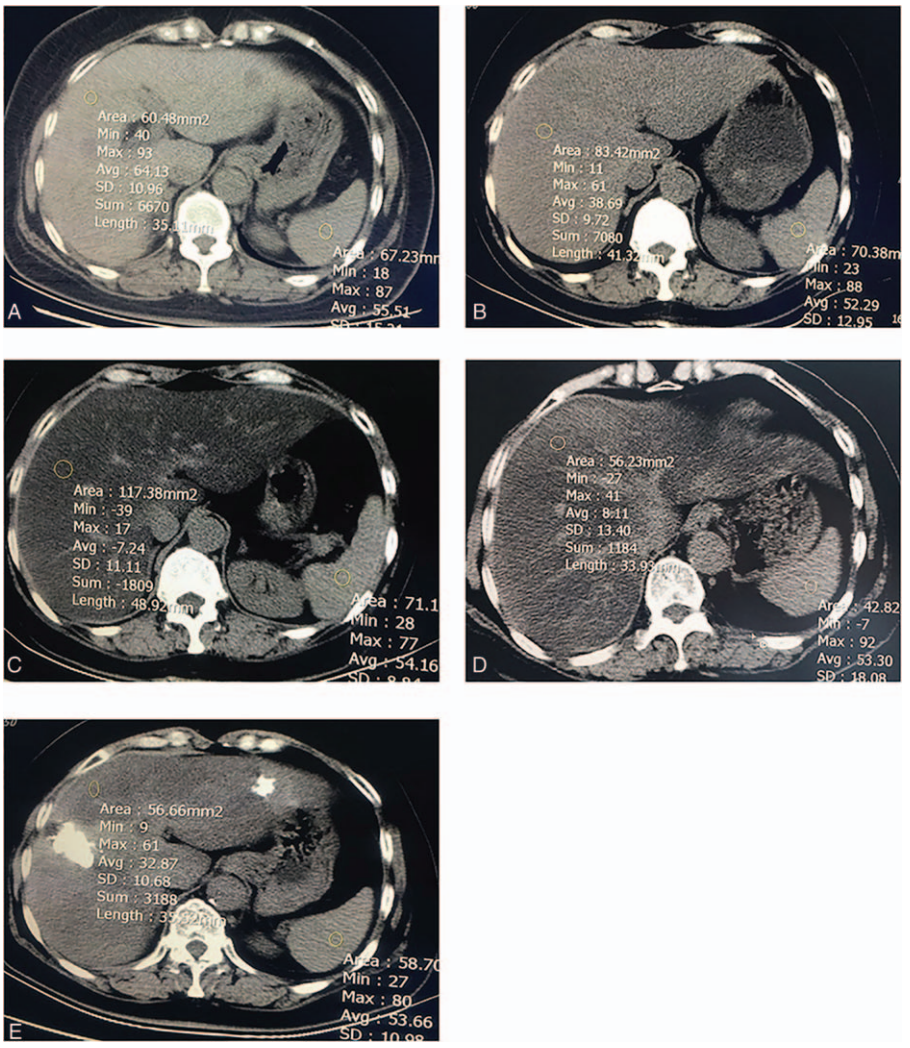

Figure 1. (A) The liver-to-spleen CT ratio (L/S ratio) of 1.16 (64.13/55.51) upon the onset of CAP regimen. (B) The liver-to-spleen CT ratio (L/S ratio) of 0.74 (38.69/52.29) after a 3-cycle course with CAP. (C) The L/S ratio of –0.13 (–7.24/54.16) after a 10-cycle course with CAP. (D) The L/S ratio returned to 0.15 (8.11/53.3) after 5 months withdrawal. (E) The L/S ratio of 0.61 (32.87/53.66) after 12 months withdrawal.

(Fig. 1D) and 0.61 (32.87/53.66) (Fig. 1E) after 5 and 12 months, respectively. Currently, the patient is continually on endocrine therapy with an optimal general status.

Approval for the study by the Ethics Committees of the First Affiliated Hospital of Wenzhou Medical University was not required because it was a case report. The patient provided written informed consent.

3. Discussion

During the clinical practice, the toxic effects of CAP were speculated as secondary to phosphorylation of 5-FU in the digestive tract.[11] Although CAP was extensively metabolized by the liver, hepatopathy with respect to the CAP or 5-FU was uncommon, which might be caused by the brief half-life period and rapid metabolism of the drug.[9] The abnormality may be restricted to the increased liver functional parameters, comprising of TB, ALT, AST, and ALP.[12] Twelves et al[13] identified that mild-to-moderate hepatic dysfunction did not significantly influence the clinical pharmacokinetic parameters of CAP and their metabolites.

Nevertheless, the patient in our case developed fatty liver, which was an extremely rare hepatic adverse reaction caused by CAP. Ipso facto, Gurzu et al[14] published a lethal case, wherein the patient suffered from multiple system failures involving steatohepatitis within the combined therapy of CAP and oxaliplatin. However, this hepatotoxicity was induced by oxaliplatin instead of CAP, as it could be prevented through the supplementation of S-adenosylmethionine in patients treated with oxaliplatin-based regimen.[15] To the best of our knowledge, the fatty liver was not reported previously with respect to the administration of CAP.

As the key contraindication, DPD deficiency was primarily suspected, as it could lead to severe toxicities, such as mucositis, diarrhea, neutropenia, cerebellar ataxia or cerebellar dysfunction with a standard dose of CAP,[16] and other unpredictable results. Moreover, our patient did not show any common signs of severe side effects based on medical history and physical and laboratory examinations. Furthermore, the search for a DPD mutation was negative. In addition, the fluoropyrimidine toxicity was partially analyzed by mutations in the coding region of *DPYD*, although deep intron mutations might influence the splicing of DPPD pre-mRNA.[17] Remarkably, the normal 5-FU pharmacokinetics or wild-type *DPYD* genotype was discovered in some patients who suffered from severe adverse reactions caused by 5-FU,[18] and thus, the negative findings for DPD deficiency might not exclude all the 5-FU related toxicity.

Moreover, the pathogenesis of nonalcoholic fatty liver disease showed an independent association with dyslipidemia, especially hypertriglyceridemia,[19] which was a rare adverse effect of CAP therapy with chronic progression. Severe hypertriglyceridemia had been shown to be associated with severe complications such as acute pancreatitis or arterial vascular events.[20,21] However, the current case could not be elucidated by this phenomenon. The fasting lipid profile of the patient revealed a normal of TC and TG content before or during the treatment, which precluded the diagnosis of hypertriglyceridemia.

To the best of our knowledge, hitherto, no cases with CAP-induced fatty liver have been reported. The mechanism may not ascribe to DPD deficiency, CAP-associated hypertriglyceridemia, or improper clinical application, although we cannot exclude the 5-FU related toxicity. Therefore, physicians should be aware of this potential hepatic hazard, and a close monitoring of the liver is recommended. Hence, the damage is reversible if only we discontinue the treatment immediately upon the appearance of signs of fatty liver.

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