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Brief communication (Original)

Imatinib-induced subclinical liver injury: histological changes of non-tumorous hepatic parenchyma

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Background: Severe clinical hepatitis after imatinib treatment has been reported anecdotally. Hepatic tissue of patients with liver matastasis is often fragile and difficult to handle during liver resection from gastrointestinal stromal tumor (GIST).

Objective: Observe hepatic tissue of these patients and examine the detailed histopathology underlying the change in the texture of non-tumorous hepatic parenchyma of these patients.

Materials and methods: We reviewed six GIST patients with liver metastases who underwent hepatic resection at King Chulalongkorn Memorial Hospital between July 2004 and November 2005. Four patients did not have imatinib and two patients received imatinib for four and eight months before liver resection. Preoperative hepatic biochemistry profiles of all patients were unremarkable. We examined histopathology of non-tumorous hepatic parenchyma of these patients using H-E staining, and additional histochemistry for vascular endothelial growth factor and epidermal growth factor receptor using immunohistochemistry staining.

Results: In all patients, common histopathological changes were swelling of hepatocytes, diffuse parenchymal congestion, dilatation of central vein, and infiltration of portal tract by mononuclear cells. However, there was significant zone 3 hepatocytolysis only in patients who received imatinib treatment. Additionally, moderate degree of hepatic steatosis correlated well with the duration of imatinib exposure. Immunohistochemical study could not demonstrate any difference between these two groups.

Conclusion: In two cases of subclinical hepatotoxicity from exposure to imatinib, histopathologic findings were consistent with drug induced liver injury. Imatinib induced liver injury may be more common than obvious clinical hepatitis.

Keywords: Gastrointestinal stromal tumor, imatinib, liver injury

Imatinib is an inibitor of Bcr-Abl tyrosine kinase. It is the only effective and approved systemic agent for the treatment of patients with advanced gastrointestinal stromal tumors (GISTs) [1] and chronic myeloid leukemia [2]. Imatinib is largely metabolized in the liver by cytochrome P4503A4 (CYP3A4) system, and has an active metabolite half-life of approximately 40 hours [3]. Up to 4% patients receiving standard dose of imatinib could have aminotransferase elevation [4]. Few reports have described hepatitis ranging from mild form to fatal hepatic necrosis in patients with chronic myeloid leukemia who received imatinib [4-8]. Nevertheless, advanced GIST patients with impaired liver function benefited from imatinib and steroid treatment [9, 10].

Hepatic tissue of patients with liver metastasis is often fragile. Then, it is difficult to handle the hepatic tissue during liver resection from gastrointestinal stromal tumor (GIST) in patients who had imatinib. In this study, we observed that the non-tumorous part of the liver appeared unusually fragile in six GIST patients with liver metastasis undergoing hepatic resection. To explain the apparent change in the hepatic tissue texture, we examined histopathology and immunohistochemistry of the non-tumorous hepatic parenchyma, comparing them with those who did not receive imatinib.

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Material and method

We reviewed six GIST patients with liver metastasis who underwent hepatic resection at Department of Surgery, King Chulalongkorn Memorial Hospital between July 2004 and November 2005. Four patients did not receive imatinib, and two patients received imatinib for four and eight months. In the group without imatinib, liver metastasis was synchronous in one patient and metachronous in the rest. In the case of synchronous tumor, the primary tumor was at the second part of duodenum. In the group with imatinib, all patients had local recurrence (one in the small bowel and another in the pelvis) and metastasis. All liver metastasis in both groups were single lesions. Preoperative hepatic biochemistry profiles in all patients were unremarkable. Viral hepatitis profiles were negative in all patients. In both groups, curative hepatic resection was performed and the local recurrence, when present, was widely excised.

We examined histopathology of non-tumorous hepatic parenchyma in all patients using H-E staining, and additional histochemistry for vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) by immunohistochemistry staining.

Results

There were five male and one female patient. Mean age was 44 years (range: 28 to 65 years). Operative procedures in the group without imatinib were three right hepatectomy and one Whipple operation plus right hepatectomy. Small bowel resection and local excision of pelvic recurrence tumor including wedge resection of liver were carried out in the treatment group. There was no mortality in both groups.

Non-tumorous hepatic parenchyma in all patients was prepared in H-E staining. Histopathological changes in both groups were summarized in **Table 1**.

In all patients, common histopathological changes in non-tumorous hepatic parenchyma were swelling of hepatocytes, diffuse parenchymal congestion, dilatation of central vein, and infiltration of portal tract by mononuclear cell as shown in **Figure 1**.

Figure 2 shows histological changes in the treatment group. Interestingly, hepatocytolysis in zone 3 was significantly prominent. The degree of hepatic steatosis correlated well with the duration of imatinib exposure. The patient who had imatinib for eight months not only had moderate degree of hepatic steatosis but also portal fibrosis.

Further immunohistochemistry study did not demonstrate any difference between two groups. **Figure 3** shows immunohistochemistry staining for VEGF and EGFR. Interestingly, EGFR was positive in all specimens, while VEGF was positive only one in the group without imatinib and in both of the treatment group.

Table 1. Non-tumorous hepatic parenchyma histopathological changes

	Without treatment	With treatment
Cellular swelling	+	+
Diffuse congestion	+	+
Anisonucleosis	+	+
Central vein dilatation	+	+
Portal tract infiltration	+	+
Fatty changes	1	++
Hepatocytolysis around perivenular region	-	+
Portal fibrosis	-	+

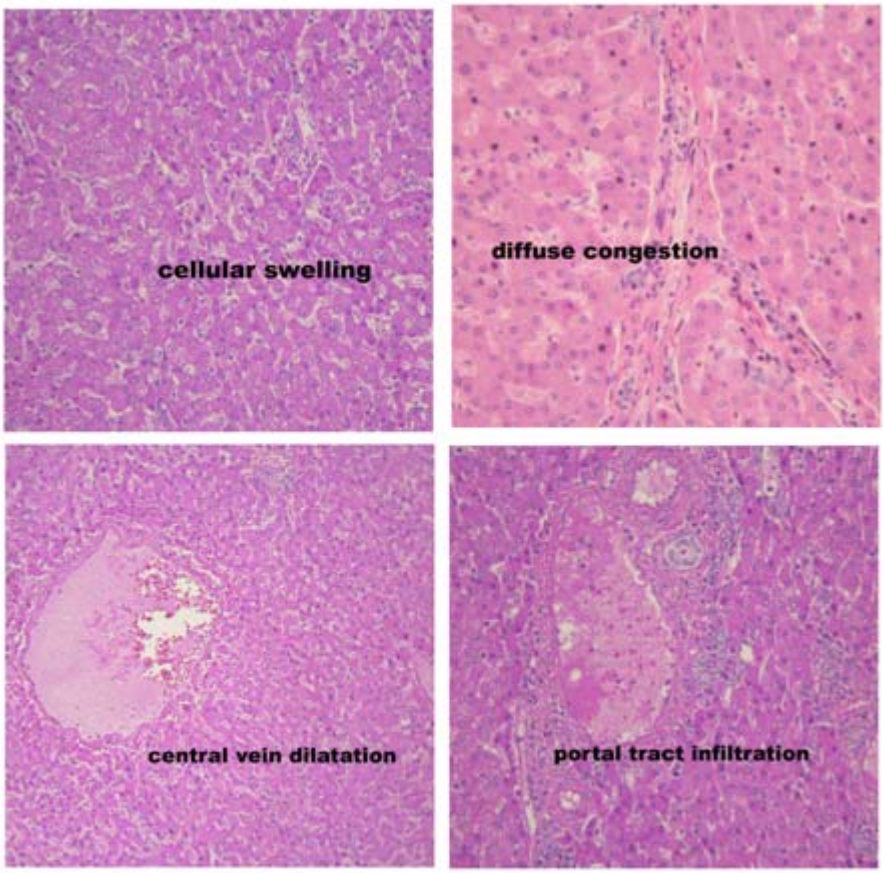

Figure 1. Common histopathological (cellular swelling, diffuse congestion, central vein dilatation, portal tract infiltration) change in all patients. H-E staining (x400).

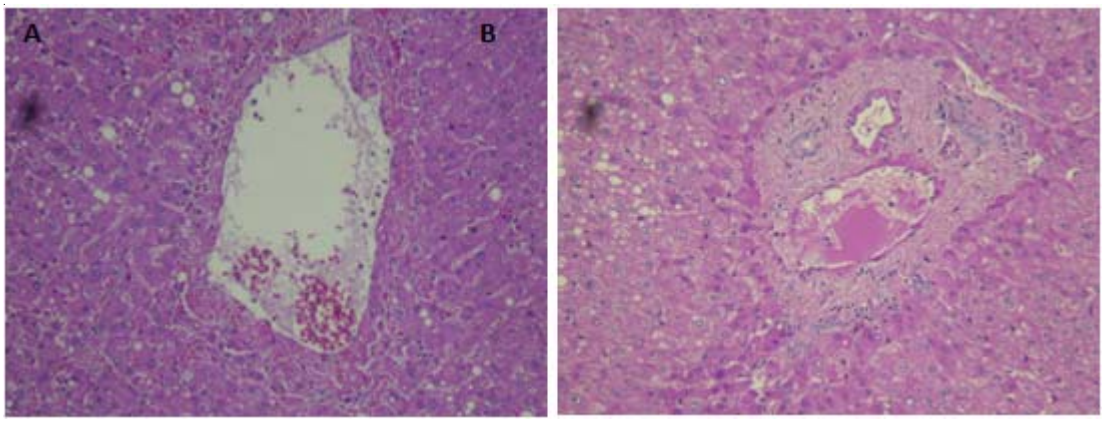

Figure 2. Hepatocytolysis around perivenular region **(A)** and portal fibrosis in the treatment group **(B)**. H-E staining (x400).

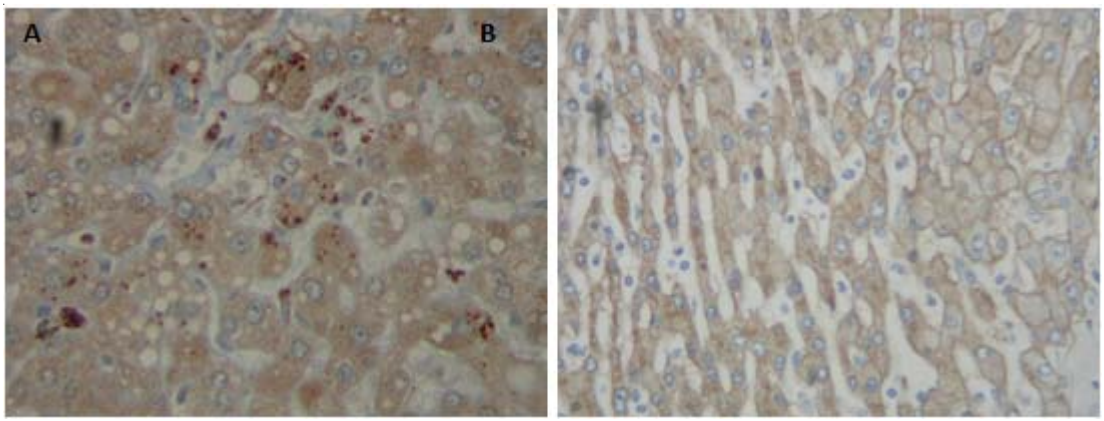

Figure 3. Immunohistochemistry staining for vascular endothelial growth factor (**A**) (x400) and epidermal growth factor receptor (**B**) (x400).

Discussion

Liver injuries with overt clinical manifestation have been reported by many authors [4-8]. In their studies, the degree of liver injuries varied from hepatitis to fatal hepatic necrosis. Kikuchi et al. [5] reported a case of severe hepatitis in a 40-year-old woman receiving 400 mg/day of imatinib for CML treatment. After 70 days of treatment, she had clinical manifestation of nausea and severe fatigue with elevation of liver enzymes and bilirubin. Neither viral hepatitis serology nor autoimmune causes could be demonstrated. Percutaneous liver biopsy revealed severe centrolobular hepatic necrosis without evidence of veno-occlusive disease. Ayoub et al. [4] also reported toxicity of imatinib in term of hepatitis, which showed marked portal tract infiltrations and mild zone 3 necrosis on liver biopsy. In addition, Ohyashiki et al. [7] described focal hepatic necrosis in the patient who was taking acetaminophen for fever during imatinib treatment. Lastly, fatal hepatic necrosis associated with this drug has been reported [6].

Swelling of hepatocytes, diffuse parenchymal congestion, dilatation of central vein and portal tract infiltration were demonstrated in both groups. Interestingly, hepatocytolysis in zone 3 was found only in the treatment group. This injury has been reported in patients who developed hepatitis while on imatinib treatment [4-8]. However, the preoperative liver biochemistries in our patients were normal. Therefore, the histopathological changes indicate the presence of hepatic injury in subclinical form. Additionally, we observed that the degree of hepatic steatosis correlated with the duration of imatinib exposure. The patient who had imatinib for eight months had greater degree of steatosis than patient with four months treatment did. These particular injuries may adversely affect the outcome, especially in hepatic resection. In our cases, the effect of subclinical hepatic injuries was not obvious due to the small amount of the resected hepatic parenchyma.

To validate whether the pathological alteration was specific to tyrosine kinase inhibitory function of imatinib, we chose to determine level of expression of potential downstream target, VEGF, and interacting pathway, EGFR, in hepatic tissue. The results did not clearly demonstrate difference of expression between treatment and non-treatment hepatocyte. Additional investigations for other markers are warranted in future studies to explain the mechanism of imatinib-induced hepatic injury.

In conclusion, imatinib exposure could induce subclinical liver injury. This injury might be more common than obvious clinical hepatitis. Its presence should be taken into consideration when major hepatic resection for metastatic GIST is planned in patients who received imatinib.

The authors have no conflict of interest to report.

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