Reversible Hepatic Steatosis in Patients Treated with Interferon Alfa-2a and 5-Fluorouracil

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Background. **Thirty previously untreated patients with metastatic colorectal carcinoma were randomized as part of two multicenter Phase III trials. Twenty-two patients were randomized to receive either 5-fluorouracil (5-FU)/interferon alfa-2A (IFN-α) or 5-FU/leucovorin (11 patients in each arm). Eight patients were randomized to receive 5-FU/IFN-α or 5-FU alone (4 patients in each arm).**

Methods. **Twenty-three patients (13 patients treated with 5-FU/IFN-α and 10 patients treated with 5-FU/leucovorin or 5-FU alone) were evaluated regularly for response by computed tomography (CT) scans of the abdomen when treatment began and then every 6–8 weeks.**

Results. **Incidentally, four patients developed hepatic steatosis during treatment with IFN-α and 5-FU. The diagnosis was based on a decreased CT value of the liver parenchyma by repeated CT scans of the abdomen during treatment, and this diagnosis was verified histologically by liver biopsy. There was no relationship to cumulative IFN-α or 5-FU dose. Based on posttreatment CT scans, the liver parenchyma changes were reversible after therapy was stopped, and there were no significant clinical sequelae. No patients treated with 5-FU/leucovorin or 5-FU alone experienced a decreased CT value of the liver parenchyma.**

Conclusion. **Hepatic steatosis was been observed in approximately 30% of patients treated with IFN-α and 5-FU. The hepatic changes were fully reversible after the treatment was stopped. Recognition of this condition is important to prevent a patient from being labeled as having progressive hepatic metastases. *Cancer* 1995;75: 2592–6.**

Key words: hepatic steatosis, colorectal carcinoma, interferon, 5-fluorouracil.

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Interferons (IFNs) are a family of naturally occurring proteins and glycoproteins that share antiviral, immunomodulatory, and antiproliferative properties.[1–3]

Three subtypes of IFNs have been identified (alfa, beta and gamma), differing in their cell surface receptors, acid stability, and amino acid sequence.[4,5]

Generally, interferon-alfa (IFN-α) is well tolerated in most widely used therapeutic doses (1–9 MIU). The most common early side effect[6–8] includes an influenza-like syndrome with fever, chills, myalgia, and headache that generally resolves spontaneously with continued administration. Patients receiving repeated doses commonly show signs of fatigue, anorexia, and weight loss. Other side effects include nausea, vomiting, diarrhea, and mild hematologic toxicity with leukopenia, thrombocytopenia, and normocytic normochromic anemia. Increased liver function parameters, especially of the transaminases and less commonly, alkaline phosphatase and lactic dehydrogenase, have been observed, but rarely necessitate dose reduction. In two studies, hepatic steatosis was reported, but its relationship to IFN-α treatment was not clarified.[9,10] It has, however, been shown that multiple cytokines, including IFN-α, can affect hepatic lipid synthesis.[11–13]

In this paper, we describe four cases of reversible hepatic steatosis that developed during treatment with IFN-α and 5-fluorouracil (5-FU) in patients with advanced colorectal cancer. The development of hepatic steatosis incidentally was found by evaluating the patients' responses.

Patients and Methods

At Odense University Hospital, 30 previously untreated patients with metastatic colorectal carcinoma were randomized in two Phase III trials comparing results of 5-FU treatment with or without INF-α 2a. Both trials were part of multicenter studies. Informed consent was ob-

tained from each patient, and the trials were approved by the Ethical Committee.

In Trial 1, the patients were randomized to receive either 5-FU/IFN-α or 5-FU/leucovorin. In the 5-FU/IFN-α regime, 5-FU was administered as a 750-mg/m^2/day dose by continuous infusion on Days 1–5, and after a 1-week hiatus, as an intravenous bolus at the same dose on a weekly schedule. Interferon-α was administered as a 9-MIU dose subcutaneously three times weekly beginning on Day 1. The 5-FU/leucovorin regime was given as a dose of 5-FU 370 mg/m^2/day intravenously and leucovorin 200 mg/m^2/day intravenously for 5 days repeated every 4 weeks. Twenty-two patients were included with 11 patients in each group.

In Trial 2, the patients were randomized to receive 5-FU/IFN-α or 5-FU alone. In both regimens, 5-FU was administered as a 750-mg/m^2/day dose by continuous infusion on Days 1–5 and then weekly as a 750-mg/m^2 intravenous bolus after a 1-week hiatus. The IFN-α was administered as a 9-MIU subcutaneous dose three times weekly beginning on Day 1. A total of eight patients were included with four patients in each group.

The regimens were continued until progression, unacceptable toxicity, or patient refusal occurred. The responses of 23 patients (13 patients treated with 5-FU/IFN-α and 10 patients treated with 5-FU/leucovorin or 5-FU alone) were evaluated regularly by computed tomography (CT) scans of the abdomen when treatment began and then every 6–8 weeks. In seven patients, response was either not evaluated by CT scans of the abdomen or CT scans were not repeated because of disease progression.

Among the four patients with hepatic steatosis, the CT scans of Patients 1 and 2 were performed using a Siemens Somatom DRG scanner (Siemens, München, Germany) producing 8-mm-thick slices, and for Patients 3 and 4, the CT scans were performed using a Philips Tomoscan LX scanner (Philips, Best, The Netherlands) producing 10-mm-thick slices. The areas of fatty liver were measured by a mean CT scan attenuation value in Hounsfield Units (HU), using unenhanced scans and standard deviations within 8–10 HU. Steatosis in liver biopsies was graded I–III, with less than one-third, one- to two-thirds, or more than two-thirds of liver cells having a fatty change.

Case Reports

Case 1

A 61-year old male with Dukes' C Stage adenocarcinoma attached to the sigmoid colon was treated with surgical resection. Because of hepatomegaly and elevated liver function parameters (transaminases, alkaline phosphatase, and lactic dehydrogenase), CT scan of the abdomen was performed showing liver metastases. The patient was treated with 5-FU/IFN-α according to Trial 1. After 174 days of treatment (cumulative dose of IFN-α = 567 MIU; 5-FU = 10.600 mg/m^2), CT scan identified a decreased attenuation of the liver parenchyma of 43–33 HU. To exclude progressive disease, a liver biopsy was performed indicating a mainly centrilobular Grade I steatosis. Treatment was stopped, and 90 days after the last treatment, CT scan identified a normalization of the CT value (47 HU). During treatment there was no radiologic change of the liver metastases, but the liver function parameters were normalized.

Case 2

A 47-year old female with Dukes' C Stage adenocarcinoma attached to the rectum and familiar adenomatosis of the colon was treated with colectomy and ileostomy. Three years after surgery, she had elevated liver function parameters. Computed tomography scan of the abdomen identified multiple liver metastases. The patient then was treated with 5-FU/IFN-α according to Trial 1. After 55 days of treatment (cumulative dose of IFN-α = 189 MIU; 5-FU = 4.400 mg/m^2), CT scan identified a decreased CT value of the liver parenchyma of 50–33 HU. Liver biopsy showed Grade II steatosis. Treatment was stopped. Control CT scan 225 days after the last treatment identified progression of the liver metastases but normalization of the CT value (52 HU). During treatment, the liver function parameters remained unchanged.

Case 3

A 53-year old male with Dukes' C Stage adenocarcinoma attached to the descending colon was treated with resection. During surgery, liver metastases were discovered and were verified histologically. To evaluate the patient's response to treatment, CT scan of the abdomen was performed showing multiple liver metastases. The patient developed an anaphylactic reaction caused by the contrast material (Hexabrix). Therefore, later scans were performed without contrast materials. The patient was treated with 5-FU/IFN-α according to Trial 2. After 28 days of treatment (cumulative dose of IFN-α = 117 MIU; 5-FU = 3.000 mg/m^2), a decreased CT value of the liver parenchyma from 48 HU to 28 HU was observed. Liver biopsy showed mainly Grade I centrilobular steatosis. Treatment was stopped, and the CT value was normalized (44 HU) 54 days after the last treatment. During treatment, liver function parameters remained normal.

Case 4

A 59-year old male with Dukes' B Stage adenocarcinoma attached to the rectum was treated with resection and sigmoistomy. During surgery, liver metastases were discovered. To evaluate the patient's response to treatment, CT scan of the

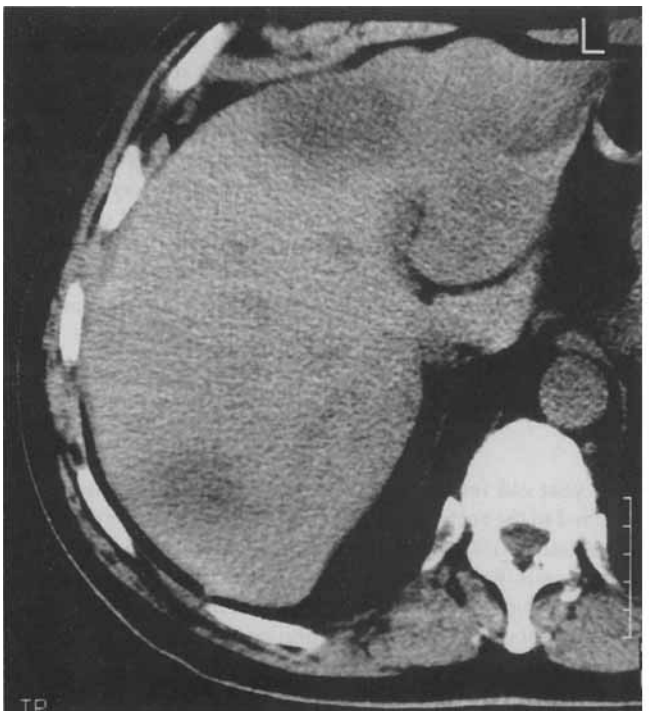

Figure 1. Case 4. Pretreatment unenhanced computed tomography scan of the liver. Between the liver metastases of low density, there is homogeneous liver tissue of normal attenuation.

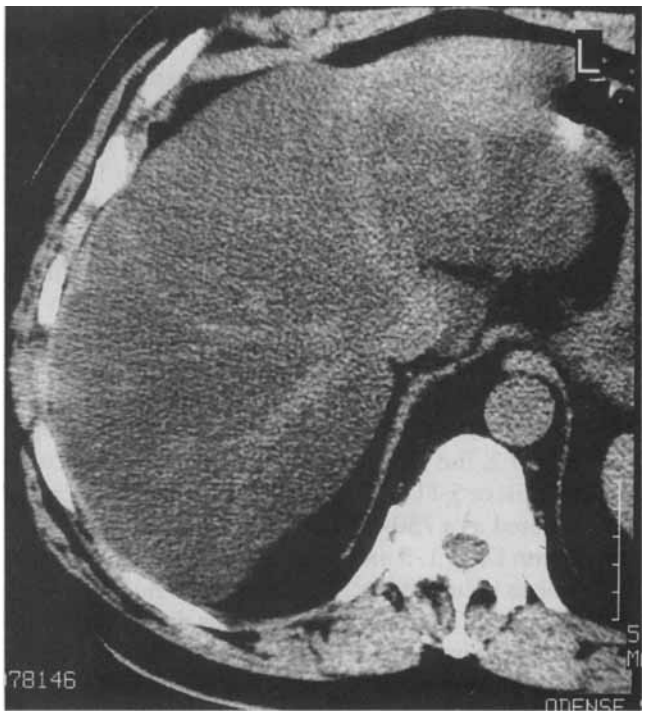

Figure 2. Case 4. After 127 days of treatment, unenhanced computed tomography scan revealed a high degree of fatty degeneration of the liver with an abnormal low density of the parenchyma (mean, 7 Hounsfield Units) and prominence of portal vessels (contrast reversal). Note the relative dense tissue (metastases) in the left hepatic lobe.

abdomen was performed (Fig. 1). The patient was treated with 5-FU/IFN-α according to Trial 2. After 127 days of treatment (cumulative dose of IFN-α = 396 MIU; 5-FU = 7.300 mg/m^2), CT scan showed a decrease in HU of the liver parenchyma from 54–7 HU (Fig. 2). Liver biopsy showed Grade III steatosis (Fig. 3). Treatment was stopped, and a control CT scan 79 days after the last treatment found an almost normalization of the CT value to 37 HU (Fig. 4). During treatment, the liver function parameters remained normal.

Discussion

By CT scan, the unenhanced normal liver is homogeneously dense, with values ranging from 50 to 70 HU, except for the portal veins, identified as linear or circular structures of lower attenuation.[14] The liver should measure 7–12 HU more than the spleen.[15] The uncontrasted CT scan is accepted as a reliable noninvasive method for a quantitative estimation of liver fat concentration.[16,17] With diffuse fatty infiltration, the hepatic density decreases to approximately 0–30 HU, and the liver attenuation is less than that of the spleen. With severe hepatic steatosis, the portal veins become more dense than the adjacent hepatic parenchyma, producing a "contrast-enhanced effect."[15,17] One study showed that the degree of fatty deposition assessed histologically correlates inversely with the measured CT numbers.[16] The most important differential diagnosis is metastases diffusely localized in the liver.[18]

Incidentally, we found that of 23 patients with metastatic colorectal carcinoma evaluated by CT scan of the abdomen, 4 of 13 patients (31%) treated with 5-FU/IFN-α and none of 10 patients treated with 5-FU/Leu-

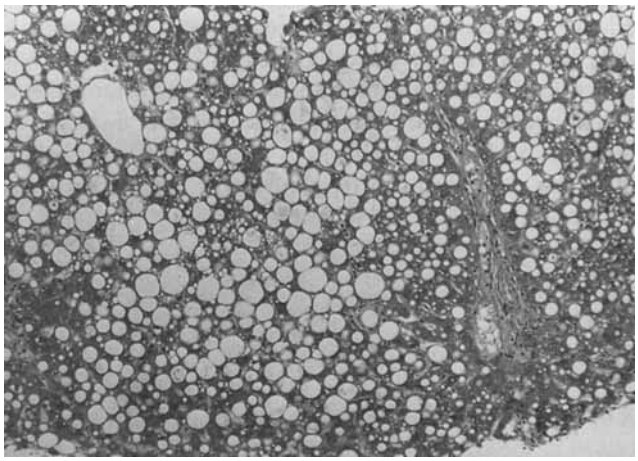

Figure 3. Case 4. Liver biopsy showing Grade III steatosis (original magnification ×150).

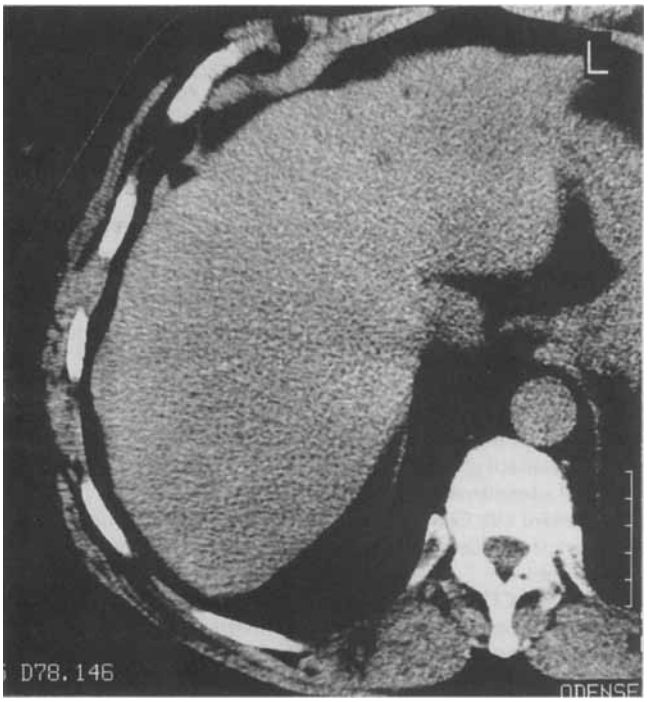

Figure 4. Case 4. Unenhanced control computed tomography scan 79 days after last treatment revealed an almost normalization of the attenuation values of the liver parenchyma (mean, 37 Hounsfield Units) with a slightly lower density of metastases and portal vessels.

covorin or 5-FU alone developed a decreased CT value of the liver parenchyma (to 7–33 HU), a median of 96 days (range, 28–174 days) after initiating treatment. To exclude progressive disease, liver biopsies were performed. All four patients showed hepatic Grade I–III steatosis. Treatment then was stopped according to the protocols. Estimated by posttreatment CT scans performed a median of 112 days (range, 54–225 days) after the last treatment, the liver parenchyma changes were completely reversible. The median cumulative dose of IFN-α was 317 MIU (range, 117–567 MIU) and of 5-FU was 6.325 mg/m^2 (range, 3.000–10.600 mg/m^2). None of the four patients were otherwise predisposed for hepatic steatosis (i.e., diabetes, alcohol consumption, obesity), and there were no changes in their medication during the treatment with IFN-α and 5-FU. Steroids were not used as antiemetics. The CT value of the liver parenchyma in the other patients was in the normal range.

The host response to cancer includes disturbances in intermediary metabolism. This is thought to be mediated by the cytokines, which are released as part of the immune response to tissue injury. Several of these cytokines, including tumor necrosis factor, interleukin 1, and IFN-α, have been shown to increase hepatic fatty acid synthesis.[11] The effect of tumor necrosis factor and interleukin 1 probably occurs by increasing hepatic citrate levels and can be inhibited by interleukin 4. The effect of IFN-α seems to be by another, yet unknown, mechanism and is not blocked by interleukin 4.[12] It is possible that these three cytokines act in synergy.[13]

In animal studies, this effect occurs within a few hours, but the result of long term administration of cytokines is not known.[11] In our material, hepatic changes already were present in the first CT scan after treatment began in two patients, but in the other two, it was first detected in the second and third scans, respectively. It must be underlined, however, that a slight degree of steatosis may be undetectable by CT scan. There was no clear relationship between the grade of steatosis and the duration of treatment, the former two patients having Grade I and II steatosis and the latter two Grade III and I steatosis, respectively.

Hepatic steatosis in patients treated with IFN was reported earlier in two studies, but its relationship to IFN was not clarified. Quesada et al.[9] found fatty metamorphosis in liver biopsies from three patients, but their pretreatment status was unknown. Eriksson et al.[10] found development of "signs" of liver steatosis by CT scan in 1 of 12 patients with malignant endocrine pancreatic tumors treated with human leukocyte IFN at daily doses of 3–6 MIU. Although the liver plays a key role in the catabolism of 5-FU, only rare reports of possible hepatotoxicity have been noted when the drug is administered alone intravenously.[19,20] However, Moertel et al.[21] found an increased frequency of liver function abnormalities in patients with colon cancer treated with adjuvant 5-FU and levamisole compared with untreated controls and patients treated with levamisole alone. In some instances, these changes were associated with fatty liver observed by CT scan or liver biopsy. The changes resolved when therapy was stopped. It is possible, but not clear, that IFN-α and 5-FU act in a similar synergistic way in producing hepatic steatosis.

In our patients, the treatment was stopped, and results of the CT scan of the liver returned to normal. Thus, the changes seem to be fully reversible. Clinicians and radiologists should be aware of this phenomenon in patients receiving IFN-α combined with 5-FU because the changes can be interpreted, incorrectly, as progressive hepatic metastasis.

References

1. Wadler S, Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: a review. *Cancer Res* 1990;50:3473–86.
2. Balkwill FR. Interferons. *Lancet* 1989;1:1060–3.
3. Krown S. Interferons in malignancy: biological products or biological response modifiers. *J Natl Cancer Inst* 1988;80:306–9.

4. Baron S, Dianzani F, Stanton GJ. General considerations of the interferon system. *Tex Rep Biol Med* 1981–82;41:1–12.
5. Baron S, Tyring SK, Fleischmann WR, Coppenhaver DH, Niesel DW, Klimpel GR, et al. The interferons: mechanisms of action and clinical applications. *JAMA* 1991;266:1375–83.
6. Renault PF, Hoofnagle JH. Side effects of alpha interferon. *Semin Liver Dis* 1989;9:273–7.
7. Itri LM. The interferons. *Cancer* 1992;70:940–5.
8. Jones GJ, Itri L. Safety and tolerance of recombinant interferon alfa-2a (Roferon-A) in cancer patients. *Cancer* 1986;57:1709–15.
9. Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU. Clinical toxicity of interferons in cancer patients: a review. *J Clin Oncol* 1986;4:234–43.
10. Eriksson B, Öberg K, Alm G, Karlsson A, Lundqvist G, Magnusson A, et al. Treatment of malignant endocrine pancreatic tumors with human leukocyte interferon. *Cancer Treat Rep* 1987;71:31–7.
11. Feingold KR, Soued M, Serio MK, Moser AH, Dinarello CA, Grunfeld C. Multiple cytokines stimulate hepatic lipid synthesis in vivo. *Endocrinology* 1989;125:267–74.
12. Grunfeld C, Soued M, Adi S, Moser AH, Dinarello CA, Feingold KR. Evidence for two classes of cytokines that stimulate hepatic lipogenesis: relationships among tumor necrosis factor, interleukin-1 and interferon-alpha. *Endocrinology* 1990;127:46–54.
13. Grunfeld C, Soued M, Adi S, Moser AH, Fiers W, Dinarello CA, et al. Interleukin 4 inhibits stimulation of hepatic lipogenesis by tumor necrosis factor, interleukin 1 and interleukin 6 but not interferon-α. *Cancer Res* 1991;51:2803–7.
14. Dick R. The liver and spleen. In: Sutton D, editor. A textbook of radiology and imaging. 5th ed. Edinburgh: Churchill Livingstone, 1993;2:949–89.
15. Sotile SC, Brogdon BG, Melham RE. Diagnostic imaging of the fatty liver. *Ala J Med Sci* 1988;25:412–6.
16. Bydder GM, Kreel L, Chapman PWG, Harry D, Sherlock S, Bassan L. Accuracy of computed tomography in diagnosis of fatty liver. *BMJ* 1980;281:1042.
17. Scatarige JC, Scott WW, Donovan PJ, Siegelman SS, Sanders RC. Fatty infiltration of the liver: ultrasonographic and computed tomographic correlation. *J Ultrasound Med* 1984;3:9–14.
18. Edal AL, Lund-Olesen LH. Focal fatty liver in ultrasound and computed tomography. *Ugeskr Laeger* 1993;155:2786–90.
19. Bateman JR, Pugh RP, Cassidy FR, Marshall GJ, Irwin LE. 5-fluorouracil given once weekly: comparison of intravenous and oral administration. *Cancer* 1971;28:907–13.
20. Menard DB, Gisselbrecht C, Marty M, Reyes F, Dhumeaux D. Antineoplastic agents and the liver. *Gastroenterology* 1980;78:142–64.
21. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA. Hepatic toxicity associated with fluorouracil plus levamisole adjuvant therapy. *J Clin Oncol* 1993;11:2386–90.