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Case Report

# Focused Radiation Hepatitis after Bragg-Peak Proton Therapy for Hepatocellular Carcinoma: CT Findings

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**Abstract:** Radiation hepatitis is clearly demonstrated by noncontrast and contrast enhanced CT following radiotherapy for liver diseases. Radiation hepatitis is dependent on dose distribution and is usually demonstrated as a nonsegmental bandlike lesion after photon therapy. We report a case of focused, oval-shaped radiation hepatitis that was induced by photon therapy. The attenuation difference was localized in a high-dose area caused by Bragg-peak proton therapy. **Index Terms:** Liver, diseases—Radiation, injurious effects—Proton therapy—Hepatitis—Computed tomography.

Focal attenuation difference of the liver on CT after radiotherapy has been recognized as radiation hepatitis (1,2). Radiation hepatitis is depicted as a hypodensity area on noncontrast CT and as a hyperdensity area on contrast enhanced CT. Typically, it is demonstrated as a lesion that is not segmentally distributed but has a wide contact with the hepatic contour. We saw oval-shaped low attenuation of the liver associated with normally arranged vasculature in a patient with hepatocellular carcinoma treated by proton radiotherapy. This unique pattern of radiation hepatitis resulted from the physical characteristics of protons and could be differentiated from abnormal density areas noted in hepatic liver scars (3) and cholangiocellular carcinomas (4).

## CASE REPORT

A 55-year-old man who had been treated for 10 years for viral hepatitis was admitted for hepatocellular carcinoma detected by ultrasonography. The tumor was located in the anterior superior segment of the right lobe of the liver. He was initially treated by transarterial chemoembolization therapy (TCE) using an oil contrast material (Lipiodol Ultra Fluid, André Gelbe Laboratory, France), and Mitomycin C (5). Computed tomography performed 3 weeks after TCE revealed several tiny deposits of oily contrast material in the liver tissue surrounding the main tumor which were strongly suggestive of an extracapsular extension of the hepatocellular carcinoma (6).

Proton therapy was recommended as an adjuvant therapy to prevent regrowth of the tumors. Proton irradiation was performed at the Proton Medical Research Center, University of Tsukuba in January 1992. In 29 days 67 Gy with 18 fractions was delivered through the anterior and right lateral portals (Fig. 1). Treatment volume included not only the main tumor but also the tiny satellite lesions distributed in its periphery. Irradiation synchronized with the respiratory cycle was used to reduce the treatment volume as much as possible (7). Proton therapy was performed without serious acute reaction including clinical radiation hepatitis except for self-limiting radiation dermatitis and mild temporary elevation of liver enzymes.

Follow-up CT was performed 3 months after completion of proton therapy. Noncontrast CT demonstrated a rectangular hypointensity with a vague contour in the right lateral portion of the liver, which corresponded to the target area irradiated with the high dose (Fig. 2a). Concavity of the contour of the liver was also demonstrated along the beam path. Single level dynamic CT and CT during arterial portography (CTAP) were performed to assess the hemodynamics of the irradiated liver as well as the effects on the tumors. In the arterial dominant phase of single level dynamic CT the target area clearly showed hyperdensity suggesting increased arterial flow (Fig. 2b). Hepatic angiography gave the same result.

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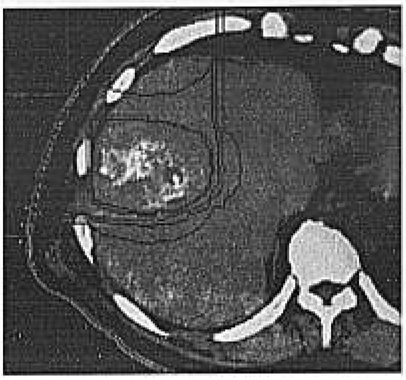

**FIG. 1.** Noncontrast CT scan performed before proton therapy for hepatocellular carcinoma (HCC). This section is immediately caudad to the lower edge of the HCC. The remnant of oily contrast media is hyperdense following embolotherapy. Isodose distributions are superimposed. Proton beams were delivered through anterior and right lateral portals. The innermost contour represents the maximum dose area (100%). The outmost black lines represent 10% isodose.

However, the area was demonstrated as hypodense on CTAP (Fig. 2c), which clearly revealed normally arranged vasculature as well. The laboratory data showed no evidence of liver dysfunction thereafter.

On CT performed 16 months after proton therapy, there was marked shrinkage of the treatment volume. The pattern of attenuation difference was the same as before, but contrast between the treatment volume and the surrounding normal liver became less distinct. Two years after proton therapy the patient is in good physical condition with no evidence of local tumor recurrence.

## DISCUSSION

The clinical picture and the histological change in the liver tissues induced by ionizing radiation are known as radiation hepatitis. Ingold et al. reported that clinical radiation hepatitis occur <60 days after completion of radiotherapy (8). The dramatic histological findings at this stage are located in the centrilobular region. They consist of severe sinusoidal congestion, hyperemia or hemorrhage, some atrophy of the central hepatic cells, and mild dilatation of the central veins with erythrocytes. These changes suggest that acute radiation hepatitis is primarily a veno-occlusive disorder. The late changes are atrophy of the centrilobular hepatic cords, minimal erythrocyte distension of the sinusoids, and thickening of the central vein wall, varying from only hyaline thickening of the endothelium to complete occlusion of the vein. Other investigators assumed that the pathogenesis of these veno-occlusive process could be explained by focal endothelial injury with focal fibrin deposition (9) or intrasinusoidal and extrasinusoidal reticulin proliferation (10).

Tomographic evaluation using CT or MRI make it possible to explain such histological changes in conjunction with topographic information (1,2). Radiation hepatitis is typically demonstrated as a sharply demarcated hypodensity from the surrounding normal liver on noncontrast CT. Unger et al. reported one case of radiation hepatitis that underwent CT arteriography (2). Our case demonstrated almost the same pattern of attenuation difference as that case, i.e., CT arteriography revealed that the region of radiation hepatitis had decreased vascular perfusion on the portal venous phase. In addition, dynamic CT showed increased attenuation of hepatic parenchyma in the areas with decreased portal perfusion on the hepatic arterial phase (11). In the case reported by Unger et al. (2) attenuation was re-

2a–c

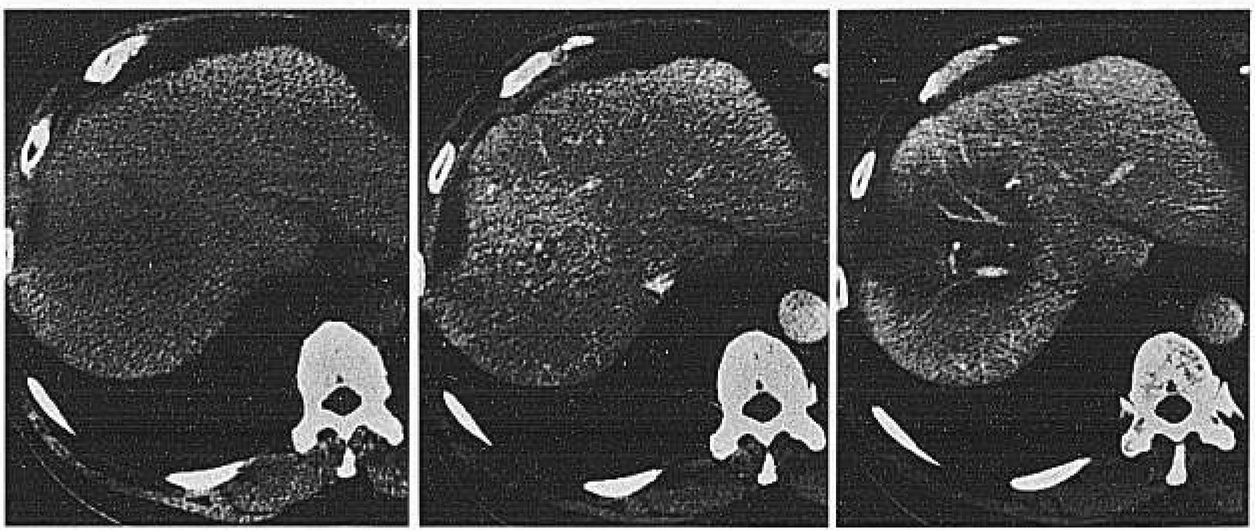

**FIG. 2.** Oval-shaped attenuation difference demonstrated on CT scans 3 months after proton radiotherapy. The target volume irradiated to a high dose is seen as a hypodense vague contour on a noncontrast CT scan **(a)**, hyperdense on arterial dominant phase dynamic CT scan **(b)**, and hypodense with a definite boundary on CT scan during arterial portography **(c)**.

versed with increased attenuation due to either increased accumulation or delayed clearance of contrast medium within the region of radiation damage on early equilibrium imaging. Unger et al. concluded that this phenomenon reflected vascular congestion and relative stasis with slow clearance of contrast media from the area of hepatic radiation damage. They also reported that MRI showed increased signal on T2-weighted imaging, reflecting increased water content in the irradiated area.

The distribution of radiation hepatitis is usually geometrical, either fan-shaped or bandlike, and corresponds to radiation portals rather than the lobar or segmental hepatic anatomy (2). The bandlike distribution reflects the dose distribution produced by photon irradiation of two opposing portals. In our case, oval-shaped attenuation difference depicted on CT corresponded to focused high-dose area produced by Bragg-peak proton therapy that is the most important characteristic of heavy particle radiation. Hence, a high-dose area does not make a wide contact with the hepatic contour and mimics a mass lesion of the liver. Proton is the commonest heavy charged particle in use clinically worldwide, although it has never been used to treat hepatic tumor. However, its use in the treatment of hepatocellular carcinoma has recently been reported (12,13).

The oval-shaped attenuation difference is a unique expression of radiation hepatitis induced by protons. Proton-inducing radiation hepatitis, however, can be distributed so that it mimicks the segmental hepatic anatomy by treatment portals. Causes of segmental hepatic abnormality include irregular fatty infiltration (14,15), acute hepatitis (3), and portal vein or biliary obstruction due to malignancy (4,16,17). Hence, proton-induced radiation hepatitis should be included in the differential diagnosis of geographic hepatic parenchymal diseases or changes.

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