Case Report

Profound Transient Thrombocytopenia Associated with ^{90}Yttrium Microsphere Therapy for Inoperable Hepatoma

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Abstract: The use of ^{90}Yttrium microspheres to treat unresectable hepatoma is increasing worldwide. Therapeutically, ^{90}Yttrium microspheres show promising increases in survival and tumor response, as well as acceptable toxicities. Here, we report on a 67-year-old man with hepatitis C-related advanced-stage hepatoma. This patient received selective internal radiation therapy (SIRT) using ^{90}Yttrium microspheres (SIR-Spheres®). The patient displayed bone marrow suppression that resulted in a transient yet profound thrombocytopenia. To our knowledge, this is the first case of a hematologic complication as a consequence of the use of commercially available ^{90}Yttrium microsphere devices.

Key Words: bone marrow suppression, hepatoma, thrombocytopenia, ^{90}Yttrium microspheres

Patients with unresectable hepatoma have limited treatment options. Of the blood supply to the hepatoma, 95% is from the hepatic artery. In contrast, the normal liver parenchyma receives only 30%, with the majority of the blood supply coming from the portal vein.[1] Transhepatic arterial chemoembolization (TACE) is widely used for hepatoma management, due to the vascular nature of hepatoma. However, TACE may increase the risk of liver failure if portal vein occlusion occurs by the invasion of the tumor. External radiation therapy is another therapeutic option for patients with advanced stage hepatoma. External radiation may cause damage to the hepatobiliary system, especially at radiation doses to the whole liver that are above 30 Gy.[2] In the past few years, the use of selective internal radiation therapy (SIRT) by ^{90}Yttrium-bearing resin or glass microspheres to treat unresectable hepatoma is increasing. ^{90}Yttrium microspheres are point sources of radiation that preferentially localize in the peritumoral and intratumoral arterial vasculature.[3] ^{90}Yttrium microspheres are delivered via the hepatic artery, and minimize the adverse effects of radiation on the normal liver parenchyma. The use of ^{90}Yttrium microspheres has been proven safe and efficacious, with limited complication shown in the literature.[4,5] Here, we report on a rare extrahepatic complication associated with bone marrow suppression that resulted in the presentation of severe thrombocytopenia.

Case Reports

A 67-year-old man was referred to the clinic due to a persistent, mild, dull pain in the right upper quadrant, accompanied by weight loss over the past month. Abdominal computed tomography (CT) discovered a large hepatic tumor with portal vein thrombosis (Fig. 1). Laboratory examination was remarkable for positive hepatitis C antibody and elevated serum alpha-fetoprotein level (90 ng/mL, normal range <8.04 ng/mL). Biopsy of the tumor revealed hepatoma. A diagnosis of advanced stage hepatoma was made, and ^{90}Yttrium microsphere therapy was performed.

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Key Points

- ^{90}Yttrium microspheres have been used to treat unresectable hepatoma.
- Radiation microsphere-induced gastrointestinal tract ulcers are the most common adverse effects.
- The severe thrombocytopenia observed one month after the treatment in this case suggests that the clinician should perform a regular hemogram check up posttherapy.

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Accepted March 4, 2010.

0038-4348/0−2000/10300-1264

(Case Report continued from previous page)

Prior to ^{90}Yttrium microsphere injection, we performed hepatic and celiac angiography to identify the hepatic artery branches and collateral vessels that were supplying the hepatoma and the gastrointestinal (GI) tract. Embolization of gastroduodenal artery with metallic coils was performed to prevent the microspheres from spreading to the GI tract and causing radiation-induced injury. Then, 99mTc macroaggregated albumin (Tc-MAA), a particulate form of albumin that mimics ^{90}Yttrium microspheres in size and density, was infused into the hepatic artery, followed by a lung scan. The lung shunting ratio was calculated at about 2%. Then 1 GBq of ^{90}Yttrium microspheres (SIR-Spheres®) was delivered into the left hepatic artery, and 2 GBq of ^{90}Yttrium microspheres were infused into the right hepatic artery. Planar scintigraphy and single-photon emission computed tomography (SPECT) were obtained the next day. These imaging methods showed an increased activity in the right lobe of the liver, without obvious tracer uptake elsewhere in the body (Figs. 2, *A* and *B*).

One month later, the patient complained of prolonged bleeding after he accidentally cut his finger. He also complained that he experienced some dyspnea upon exertion. He denied taking other drugs or having melena. A laboratory exam revealed a decreased blood cell count, especially a decrease in the number of platelets. His white blood cell count was $3.8 \times 10^3/\mu L$ (normal: 3.5×10^3 to $9.1 \times 10^3/\mu L$), hemoglobin level was 8.6 g/dL (normal: 14 to 17 g/dL), and platelet count was $4 \times 10^3/\mu L$ (normal: 157×10^3 to $377 \times 10^3/\mu L$). The patient then received 24 units of platelet concentrates for severe thrombocytopenia. Five days later, the patient's platelet count was $21 \times 10^3/\mu L$. A bone marrow biopsy performed on the same day disclosed a hypocellular marrow with about 10% cellularity (Fig. 3). No malignant cells, fibrosis, or microspheres were found in the bone marrow. Bone marrow suppression associated with the radiation effect of the ^{90}Yttrium microspheres was suggested. The patient's thrombocytopenia recovered to near pretreatment level three months later (Table).

Discussion

Radioembolization with ^{90}Yttrium microspheres and SIRT, once the microspheres are lodged at the ends of the capillaries of the hepatic parenchyma, has been shown to be effective in the treatment of unresectable hepatoma. ^{90}Yttrium microsphere treatment shows an improvement in the median survival time, and a downstage of the disease that can then be treated with other forms of therapy, including liver transplant.[4–6] ^{90}Yttrium is a pure beta ray emitter, with a half-life of 64.2 hours and an average tissue penetration of 2.5 mm (a maximum of 11 mm). There are two commercially available microsphere devices. The ^{90}Yttrium is either embedded in a 20- to 30-μm glass microsphere (TheraSphere®, MDS Nordion, Ottawa, Ontario, Canada) or 20- to 60-μm resin microsphere (SIR-Spheres®, Sirtex Medical, Sydney, Australia). A pre-therapy work up includes a diagnostic angiograph, followed by preemptive coil embolization of the collateral arteries supplying the gastroduodenal region. The reason for this embolization is to decrease GI tract complication. Tc-MAA is infused into the hepatic arteries to evaluate the degree of hepatopulmonary shunt. To avoid radiation pneumonitis, the upper limit of the hepatopulmonary shunt is 13%, and the administered dose can be reduced if the shunt level slightly exceeds 13%.[7,8]

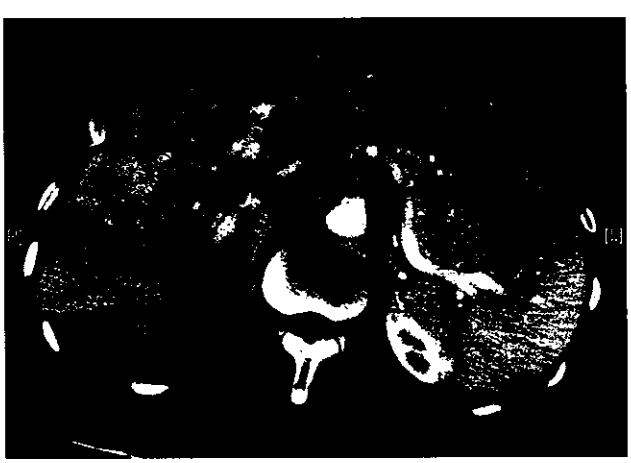

Fig. 1 Abdominal computed tomography (CT) scan (artery phase) showing a large tumor with daughter nodules over the right lobe with bilateral portal vein thrombosis.

Over the years, the use of ^{90}Yttrium microspheres to treat advanced stage hepatoma has increased in many centers worldwide. With increasing usage, more adverse effects of ^{90}Yttrium microspheres have also been found. Besides post-implant fever and abdominal pain, which may be considered an embolic effect of the microsphere, unusual radiation-induced side effects in the GI tract, the hepatobiliary system, the lungs, and the hematology system have been reported. Radiation microsphere-induced GI tract ulcers and inflammation are the most published

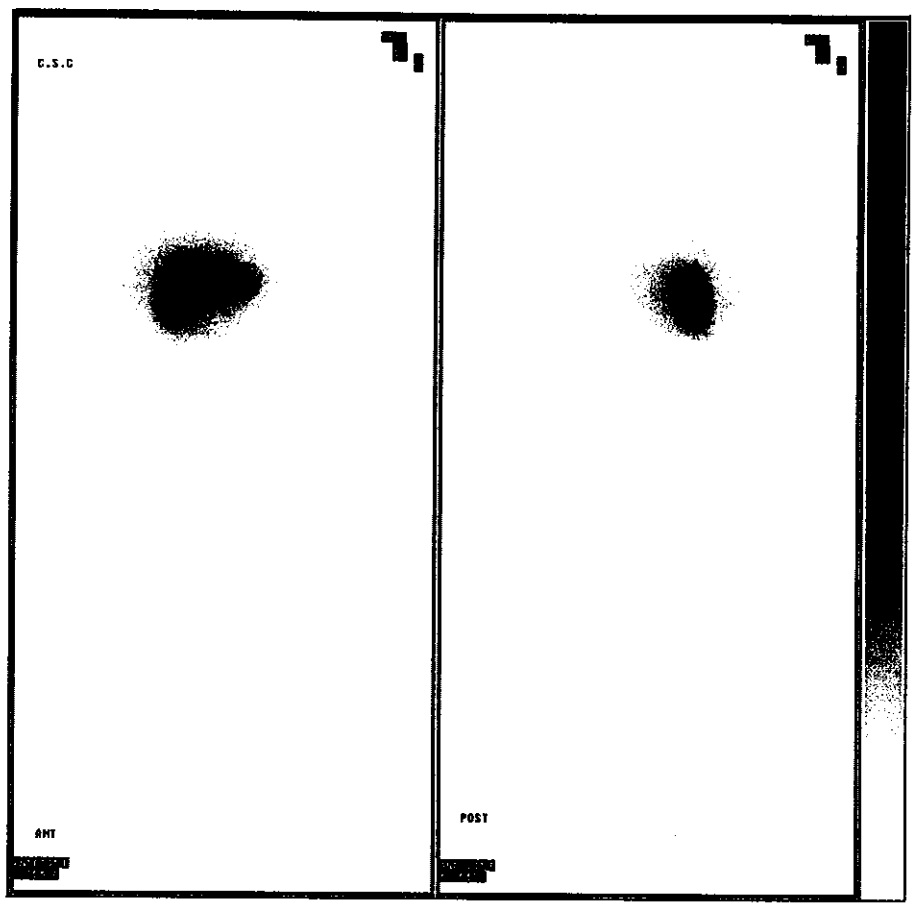

Fig. 2 **Planar scintigraph (*A*) and single-photon emission computed tomography (*B*) images obtained the day following ^{90}Yttrium microsphere infusion.**

adverse effects, with incidence of wide range from 3% to 24%.[9–14] The microspheres are thought to travel through the bloodstream to the GI tract. It has been suggested that the microspheres have these effects on the GI tract due to failure to detect the small supply vessels in the GI tract upon initial angiogram, or due to the growth of new collateral vessels post-prophylactic coil embolization.[14] Adjacent hepatic parenchyma and biliary tract injury may occur weeks to months after irradiation, and may present as a tender hepatomegaly, liver dysfunction, multiple biliary stricture, or radiation-related cholangitis of the normal biliary tree, with a reported incidence up to 14%.[15,16] Tumor-induced arteriovenous shunting can facilitate microsphere deposition in the lungs, which can result in radiation-induced pneumonitis with a reported incidence from 2.5% to 6.2%.[8,17] Therefore, it is suggested that SIRT treatment be withheld if significant lung shunting is observed by the Tc-MAA study. Furthermore, it is suggested that no more than 3 GBq of ^{90}Yttrium microspheres be injected at one session.[8,17]

A hematological adverse effect is quite rare. Carr reported one case series study of ^{90}Yttrium glass microspheres that revealed a minimal decrease in platelet and absolute granulocyte counts in some patients.[18] However, prominent lymphopenia without clinical consequence was seen in many patients. Pancytopenia was found in only one patient and was due to a degradation of the bonds between the isotope and the resin, causing the isotope to be released into circulation. This degradation in the bond occurred in one case series study where the device was laboratory-made.[19] Bone marrow suppression due to use of the current commercial devices has not been previously reported. The bone marrow suppression seen in this case study may be due to the leached ^{90}Yttrium from the resin particle because the isotope was not excreted outside of the body and was taken up by the bony tissue, resulting in a dose-related risk of marrow suppression.[20] Based on the case presented here, the clinician should be aware of the possible hematological side effect of ^{90}Yttrium microsphere therapy. Supportive treatment is safe for patients with decreased blood

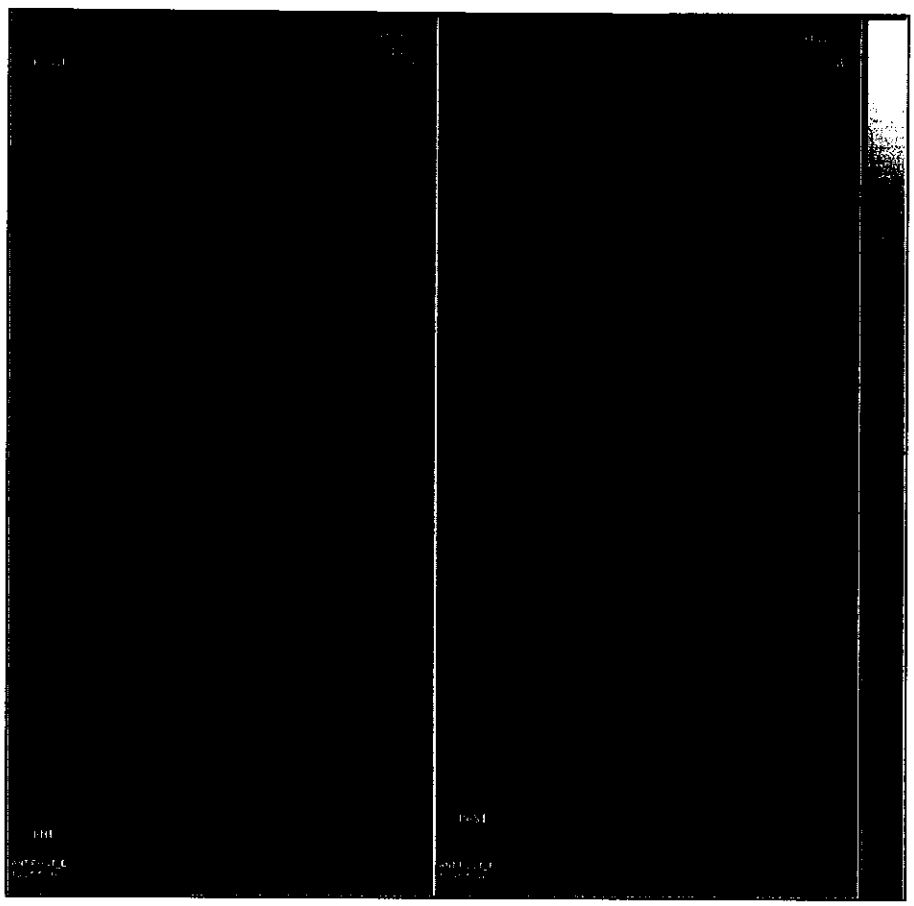

Fig. 2 Continued.

cell counts. The effect of radiation on blood cell suppression is transient, and blood cell counts will recover as the radiation effect decreases over time.

Fig. 3 Bone marrow biopsy disclosed a hypocellular marrow with few bone marrow cells (arrow; hematoxylin and eosin [H&E] stain, 100x magnification).

Conclusion

Direct intra-arterial therapy with ^{90}Yttrium microspheres is a promising method for the treatment of advanced stage hepatoma. ^{90}Yttrium microspheres exhibit less toxicity than other therapies. However, complications related to radiation dosage or potential shunting of the microspheres may occur. In addition to the commonly reported GI tract, hepatobiliary tract, and pulmonary complications, clinicians should be aware of a rare hematological complication that is associated with ^{90}Yttrium microsphere therapy.

Acknowledgments

The authors thank the hepatoma team, including Dr. Yoa-Li Chen (Department of Surgery, ChangHua Christian Hospital), Dr. Chen-Te Chou (Department of Radiology, ChangHua Christian Hospital), Dr. Quan-Zheng Wang (Department of Oncology, ChangHua Christian Hospital), and Dr. Yueh-Min Lin (Department of Pathology, ChangHua Christian Hospital) for their care of this patient.

Table. Blood cell count record[a]

No. blood cells	Pretreatment	Posttreatment					
		d 7	d 30	d 35	wk 8	wk 12	wk 27
WBC ($\times 10^3/\mu L$)	5.6	4.0	3.8	3.8	4.3	3.3	4.7
Hb (g/dL)	11.8	10.4	8.6	11.1	11.1	11.1	10.4
Platelets ($\times 10^3/\mu L$)	174	145	4	21	67	120	120

[a]*WBC, white blood cell count; Hb, hemoglobin.*

Normal WBC range: 3.5–9.1 × $10^4/\mu L$. Normal Hb range: 14.0–17.0 g/dL. Normal platelet cell count range: 157–377 × $10^4/\mu L$.

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