Original Article | Gastrointestinal Imaging

http://dx.doi.org/10.3348/kjr.2014.15.2.218
pISSN 1229-6929 · eISSN 2005-8330
Korean J Radiol 2014;15(2):218-225

Korean Journal of Radiology
KJR

Hepatic Sinusoidal Obstruction Syndrome Caused by Herbal Medicine: CT and MRI Features

Hua Zhou, MMed[1], Yi-Xiang J. Wang, MMed, PhD[2], Hai-yan Lou, MD[1], Xiao-jun Xu, PhD[3], Min-ming Zhang, MD, PhD[3]

[1]Department of Radiology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China; [2]Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR 999077, China; [3]Department of Radiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, China

Objective: To describe the CT and MRI features of hepatic sinusoidal obstruction syndrome (HSOS) caused by herbal medicine *Gynura segetum*.

Materials and Methods: The CT and MRI features of 16 consecutive *Gynura segetum* induced HSOS cases (12 men, 4 women) were analyzed. Eight patients had CT; three patients had MRI, and the remaining five patients had both CT and MRI examinations. Based on their clinical presentations and outcomes, the patients were classified into three categories: mild, moderate, and severe. The severity of the disease was also evaluated radiologically based on the abnormal hepatic patchy enhancement in post-contrast CT or MRI images.

Results: Ascites, patchy liver enhancement, and main right hepatic vein narrowing or occlusion were present in all 16 cases. Hepatomegaly and gallbladder wall thickening were present in 14 cases (87.5%, 14/16). Periportal high intensity on T2-weighted images was present in 6 cases (75%, 6/8). Normal liver parenchymal enhancement surrounding the main hepatic vein forming a clover-like sign was observed in 4 cases (25%, 4/16). The extent of patchy liver enhancement was statistically associated with clinical severity classification (kappa = 0.565).

Conclusion: Ascites, patchy liver enhancement, and the main hepatic veins narrowing were the most frequent signs of herbal medicine induced HSOS. The grade of abnormal patchy liver enhancement was associated with the clinical severity.

Index terms: *Hepatic sinusoidal obstruction syndrome; Herbal medicine; Pyrrolizidine alkaloid; Computed tomography; Magnetic resonance imaging*

INTRODUCTION

Hepatic sinusoidal obstruction syndrome (HSOS), formerly called hepatic veno-occlusive disease, is a rare yet life-threatening clinical syndrome characterized by painful hepatomegaly, ascites and hyperbilirubinemia (1). This disease was first described in 1920 in association with the ingestion of Senecio tea containing natural toxin pyrrolizidine alkaloids (PAs) (2). Since then, many cases being induced by PAs-containing herbal medicines or food contaminated with PAs in countries such as South Africa, Afghanistan and Spain (3-5) have been reported. Currently, the most important and frequent cause of HSOS in Europe and the US is the use of high-dose chemotherapy in recipients of hematopoietic stem cell transplantation, along with many other factors in the pathogenesis of HSOS, including alcohol, oral contraceptives, and radiation injury (6-8). Recently, HSOS induced by PAs-containing *Gynura*

Received February 18, 2013; accepted after revision December 7, 2013.

Corresponding author: Min-ming Zhang, MD, PhD, Department of Radiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou 310009, China.
• Tel: (86571) 87315255 • Fax: (86571) 87315255
• E-mail: zhangminming@zju.edu.cn

Korean Journal of Radiology
KJR

segetum (Tusanqi), a traditional herbal medicine used for treating traumatic injury, is increasingly being reported (9-11).

For patients who received stem cell transplantation, the diagnosis of HSOS is usually based on signs and symptoms, and clinical criteria have been formalized by investigators from Baltimore and Seattle (12, 13). For patients without stem cell transplantation treatment, especially those induced by herbal medicine, the diagnosis is difficult since PAs exposure can be obscure and the clinical presentations usually mimic other liver disorders. For these cases, a detailed history as well as radiologic evaluation can play important roles in diagnosing this disease. To dates, the reports of radiologic features of HSOS, both related and unrelated to herbal medicines, have been limited (14-17). The aim of this paper is to describe the CT and MRI features of 16 cases of HSOS caused by herbal medicine *Gynura segetum*.

MATERIALS AND METHODS

Patients

All data were obtained from a single center. Approval for retrospective analysis of the patient data was obtained from our hospital ethics committee while the patients' informed consent was waived. Eighteen cases diagnosed as *Gynura segetum* induced HSOS from August 2009 to February 2011 in our hospital were retrieved through a computerized search of medical records. Based on a previously study (18), the inclusion criteria were 1) the patients met the modified Seattle criteria (19) for HSOS characterized by hyperbilirubinemia, hepatomegaly and weight gain due to fluid accumulation, 2) a Roussel Uclaf Causality Assessment Method score ≥ 5 (20), and 3) a history of ingestion of *Gynura segetum*. All patients did not have a liver disease before their intake of *Gynura segetum*, and they were confirmed not to have viral hepatitis, Budd-Chiari syndrome, alcoholic cirrhosis, cholestasis secondary to sepsis, tumour infiltration, or congestive heart disease. Two patients without CT or MR examination were excluded. The remaining 16 cases composed the current study series, including 12 men and 4 women (age range, 22–72 years; mean age, 55.6 years). No patients had received stem cell transplantation or chemotherapy. One patient underwent subsequent liver transplantation after HSOS diagnosis. The interval between *Gynura segetum* consumption and initial CT or MR examination ranged from 1 month to 6 months (mean, 3.2 months).

Based on a classification widely used for retrospective assessment (21), the patients were clinically classified into three groups based on the severity of disease and the outcome: one case being mild, whose disease was clinically obvious, but resolved without treatment; seven cases being moderate, whose symptoms required diuretics or pain medication; eight cases being severe, whose disease required treatment and did not resolve after 100 days' treatment, or led to mortality (Table 1).

Imaging Technique

For the initial examination, eight patients had CT, three patients had MRI, while the remaining five cases had both CT and MRI. Moreover, one case had CT angiography and seven cases had MR angiography for evaluation of hepatic vein, portal vein and inferior vena cava. Liver CT and MR examination followed the routine protocols at our hospital. CT was performed with a 16-slice CT scanner (Aquilion 16; Toshiba Medical Systems, Otawara, Japan) with the following scanning parameters: 120 kVp, 200 mAs, and 5 mm slice thickness. After noncontrast scan, triphasic contrast-enhanced CT was performed after injection of 100 mL iodinated contrast medium (iopromide, Ultravist 300; Schering, Berlin, Germany) with an automatic power injector at a rate 3 mL/sec. Images were obtained in arterial, portal venous, and hepatic venous phases, respectively, with 25–30 seconds, 55–70 seconds, and 90–110 seconds start delays after initiation of the contrast medium injection. CT angiography was performed using the same CT scanner with a thickness of 0.625 mm. Three-dimensional (3D) and multiple planar reconstruction (MPR) were generated at a workstation (Vitrea 2, Vital Images, Minnetonka, MN, USA).

Magnetic resonance imaging was performed with a 1.5T scanner (seven cases; Signa Excite; GE Medical Systems, Milwaukee, WI, USA) or a 3.0T scanner (one case, Signa HDxt; GE Medical Systems, Milwaukee, WI, USA). Precontrast sequences included coronal fast imaging employing state acquisition sequence, T2-weighted fast fat-suppressed spin-echo images (T2WI), and T1-weighted gradient-echo images (T1WI) with dual-echo acquisition. Dynamic contrast-enhanced T1-weighted fast spoiled gradient-recalled echo images were obtained with delays of 45–60 seconds and 90–120 seconds, respectively, after a bolus injection of 0.1 mmol/kg of Omniscan (GE Healthcare, Cork, Ireland). MR angiography was performed using the 1.5T scanner and with the following parameters: repetition time (msec)/echo time (msec) = 4.8–7.0/1.1, 256 x 128 matrix, 26–36 cm field

Table 1. Summary of Patient Clinical Classification and Imaging Findings during Initial Presentation

Patient NO./ Age (yr)/Sex	Clinical Classification	PE Severity	Hepatomegaly	HVN	GWT	Ascites	Clover Sign	HI	PC	Follow-Up Images
Case 1/68/F	Moderate	Grade 3	+	+	+	+	-	NA	NA	-
Case 2/72/M	Moderate	Grade 2	-	+	+	+	-	NA	NA	-
Case 3/68/F	Severe	Grade 3	+	+	+	+	-	NA	NA	+
Case 4/45/M	Severe	Grade 3	+	+	+	+	+	+	+	-
Case 5/47/M	Severe	Grade 2	+	+	-	+	+	+	+	-
Case 6/67/M	Severe	Grade 3	-	+	+	+	-	-	+	-
Case 7/25/F	Mild	Grade 1	+	+	+	+	-	+	-	+
Case 8/45/F	Moderate	Grade 2	+	+	+	+	-	-	-	+
Case 9/75/M	Moderate	Grade 1	+	+	+	+	-	NA	NA	-
Case 10/47/F	Severe	Grade 3	+	+	+	+	-	NA	NA	-
Case 11/65/M	Moderate	Grade 3	+	+	+	+	-	NA	NA	-
Case 12/22/M	Severe	Grade 3	+	+	+	+	-	-	+	-
Case 13/62/M	Severe	Grade 3	+	+	+	+	-	NA	NA	-
Case 14/46/M	Moderate	Grade 2	+	+	-	+	-	NA	NA	-
Case 15/57/M	Moderate	Grade 2	+	+	+	+	+	-	+	+
Case 16/47/M	Severe	Grade 3	+	+	+	+	+	+	+	+
Incidence of imaging findings (%)		100	87.5	100	87.5	100	25	50	75	

Note.— MR was not performed in 8 cases; therefore heterogeneous intensity and periportal cuffing were not applicable for these cases. GWT = gallbladder wall thickening, HI = heterogeneous intensity on T2-weighted image, HVN = hepatic vein narrowing, NA = not applicable, PC = periportal cuffing, PE = patchy enhancement

of view, 45–60° flip angle, 2.5–3.0 mm section thickness. 3D and MPR image were reformatted at a workstation (Advantage Windows 4.2_03; GE Healthcare, Milwaukee, WI, USA).

Imaging Analysis

All CT and MR images were reviewed by two experienced radiologists, who were blind to the clinical information. Based on the published literatures (15-17, 22) and our own experience, the following abnormal findings were assessed, i.e., hepatomegaly (> 18 cm; craniocaudally), hepatic vein narrowing, gallbladder wall thickening (> 3 mm), ascites, and patchy enhancement. Because the main right hepatic vein is usually the largest of the three main hepatic veins and the middle and the left ones frequently form a common trunk (23, 24), we measured the main right hepatic vein in hepatic venous phase images and defined its diameter < 1.5 mm as hepatic vein narrowing (23). For the cases with MR images, we analyzed the liver parenchyma signal and recorded the cases showing high intensity surrounding portal vein in T2-weighted image, which have been named "periportal cuffing" sign (15). The final interpretation was reached by consensus between the two radiologists while a third investigator took part in the arbitration when consensus could not be reached.

Furthermore, in order to assess the extent of patchy liver enhancement on post-contrast CT and MRI, we classified the severity of abnormal enhanced areas on a 3-point ordinal scale (Fig. 1): grade 1 = slight patchy enhancement visible in minority sections, grade 2 = coalescent or diffuse patchy enhancement in majority sections, and grade 3 = diffuse patchy enhancement visible on all sections of the liver.

Statistical Analysis

The prevalence of imaging findings was estimated as a percentage of the patients displaying each abnormality. Association between the extent of the patchy liver enhancement and clinical classification was assessed using kappa test. Statistical analysis were performed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 summarized the imaging findings during the initial examinations. Ascites and patchy liver enhancement were the two most common radiologic findings in HSOS, both of which were present in all cases (16/16, 100%) (Fig. 2). In 10 cases, the main right hepatic vein was visible

Korean Journal of Radiology
KJR

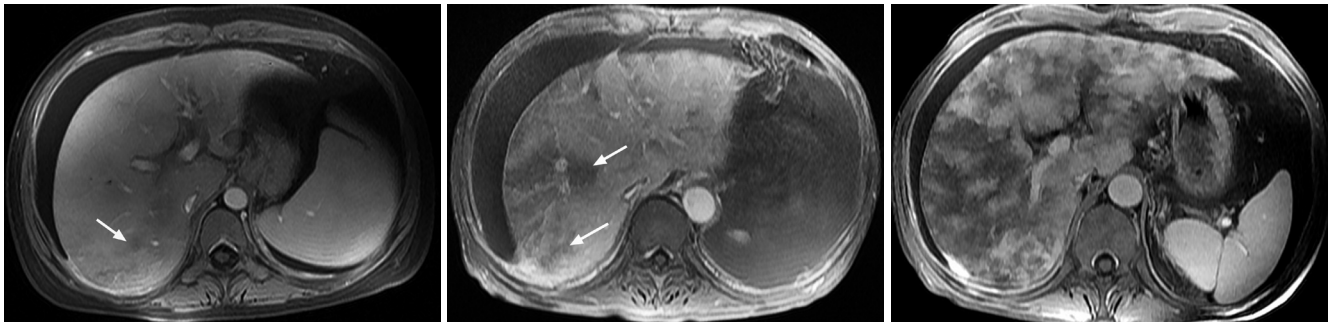

Fig. 1. Post contrast-enhanced MR images show severity of patchy liver enhancement in hepatic sinusoidal obstruction syndrome.
A. Grade 1. Arrow denotes mild patchy enhancement. **B.** Grade 2. Arrows denote moderate confluent patchy enhancement. **C.** Grade 3. Severe case with diffuse confluent patchy enhancement. Note all three cases demonstrate ascites.

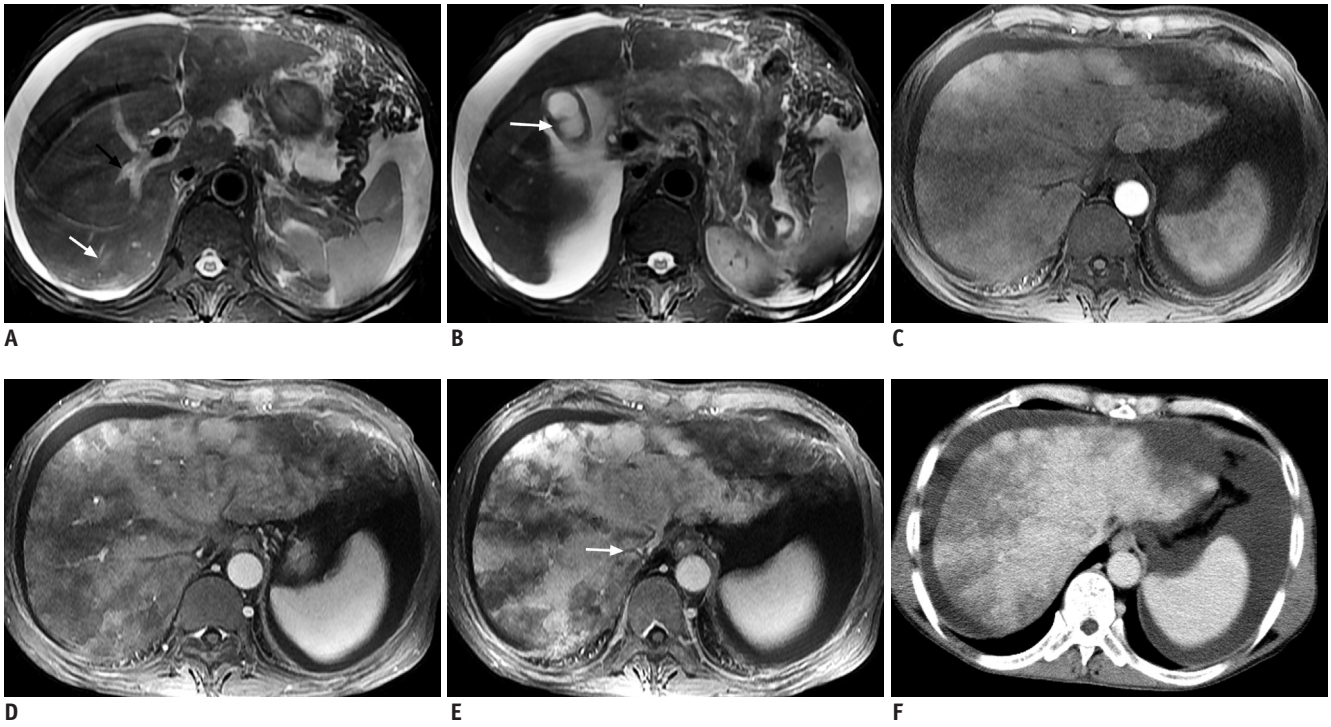

Fig. 2. 57-year-old man diagnosed with hepatic sinusoidal obstruction syndrome two months after ingestion of *Gynura segetum*.
A. Periportal cuffing (black arrow) and subtle parenchymal heterogeneity (white arrow) are demonstrated on fat-suppressed T2-weighted MRI. **B.** Gallbladder wall thickening (arrow) is also demonstrated. **C-E.** Patchy enhancement is well demonstrated on T1-weighted gadolinium-enhanced MRI (**C**: artery phase, **D**: portal phase, **E**: hepatic venous phase), especially on portal and hepatic venous phase. Note middle and left main hepatic vein are narrowed, while right main hepatic vein is unenhanced (arrow). **F.** Hepatic venous phase CT from same patient also demonstrates patchy liver enhancement.

and measured to be less than 1.5 mm. For the remaining 6 cases, the main hepatic veins were unenhanced on sectional imaging, and even difficult to visualize with CT angiogram (n = 1) or MR angiograms (n = 7).

Hepatomegaly and gallbladder wall thickening were the second most common findings in HSOS, both of which were present in 14 cases (14/16, 87.5%) (Fig. 2). Out of the eight cases who had MRI, heterogeneous intensity and periportal cuffing were detected in four (4/8, 50%) and six cases (6/8, 75%), respectively, on T2-weighted images.

An interesting sign was detected in four cases (4/16, 25%). In hepatic venous phase CT or MR images, liver parenchyma surrounding the main hepatic vein presented relatively normal enhancement and was highlighted in the background of decreased patchy enhancement elsewhere (Fig. 3). Given the special shape of the enhancement, “clover sign” was coined to describe the interesting presentation.

On post-contrast CT or MR images, based on the extent

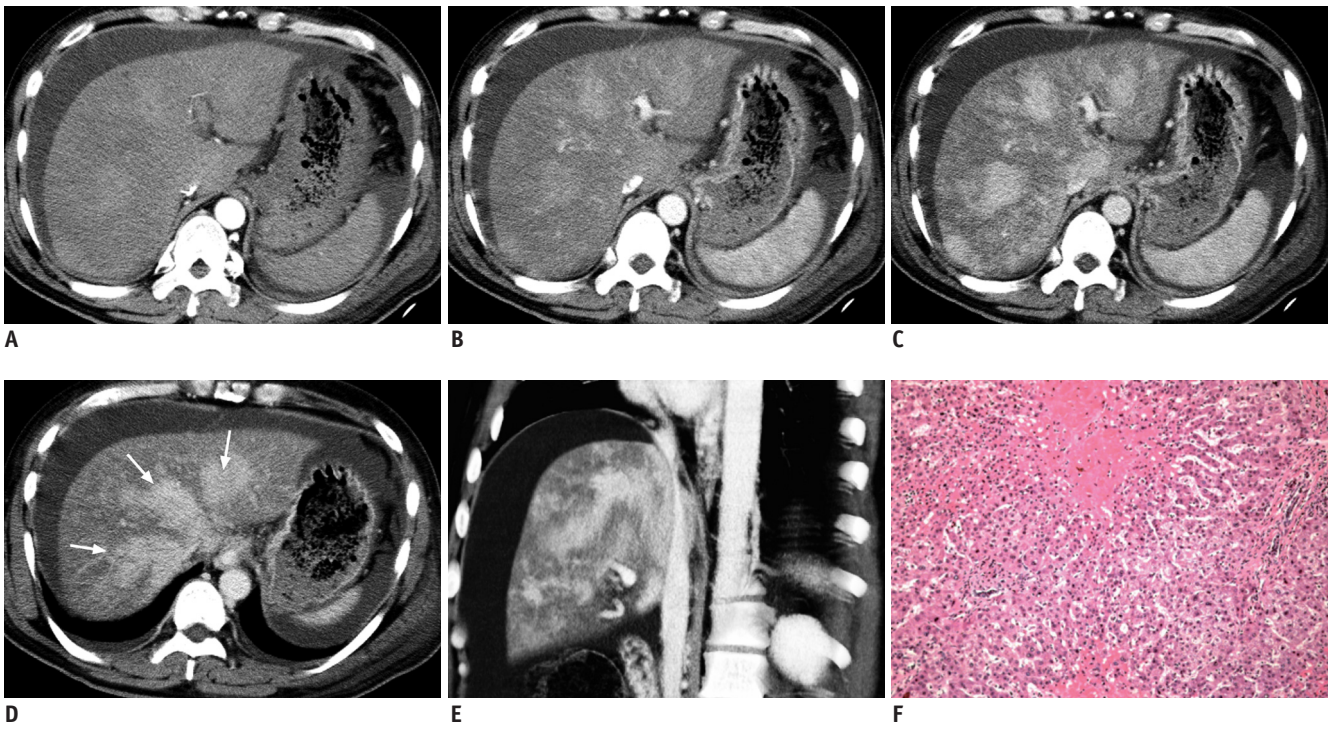

Fig. 3. 49-year-old man diagnosed with hepatic sinusoidal obstruction syndrome two months after ingestion of *Gynura segetum*. **A-C.** Arterial, portal and hepatic venous phase CT scans demonstrate patchy liver enhancement. **D.** Clover-like enhancement surrounding hepatic veins is well demonstrated at hepatic venous phase on slice through hepatic vein level (arrows). **E.** Multiple planar reconstruction CT angiogram shows that inferior vena cava is slightly compressed by swelling liver while still remain patent. **F.** Pathologic hematoxylin and eosin staining (x 100) from liver transplantation demonstrates sinusoidal congestion, centrilobular hepatocytes necrosis and slight fibrous hyperplasia in portal area.

Table 2. Association between Extent of Patchy Liver Enhancement and Clinical Classification

Clinical Classification	Extent of Patchy Liver Enhancement			
	Grade 1	Grade 2	Grade 3	Total
Mild	1	0	0	1 (6%)
Moderate	1	4	2	7 (44%)
Severe	0	1	7	8 (50%)
Total	2 (13%)	5 (31%)	9 (56%)	16

Note.— Data are numbers of cases. Significant association existed between extent of patchy liver enhancement and clinical classification (kappa = 0.565).

of unenhanced patchy area of liver, 2, 5, and 9 cases were radiologically scored as grade 1, grade 2, and grade 3, respectively (Table 2). There was a significant association between the extent of patchy liver enhancement and the clinical severity classification (kappa = 0.565).

For 8 cases with CT angiography or MR angiography, there was no evidence of occlusion of vena cava while the hepatic segment of vena cava could be compressed by swelling live (Fig. 3).

For the patients who had been treated with liver transplantation, pathological section demonstrated sinusoidal congestion, centrilobular hepatocytes necrosis, and slight fibrous hyperplasia in the portal area (Fig. 3).

Five patients had follow-up CT or MR examination with an interval ranging from 15 days to 2 months. Of these follow-up cases, imaging findings were mild (grade 1) in one, moderate in two (grade 2), and severe in two (grade 3), during the initial examination. The imaging findings resolved in one patient with mild findings at one month follow-up examination, while no radiologic improvement was found in the remaining four cases.

DISCUSSION

Although the majority of HSOS in published literatures were caused by myeloablative “conditioning regimens” after

Korean Journal of Radiology
KJR

stem cell transplantation, PAs was among the first identified toxins that can injure liver sinusoidal endothelium (11). An animal study revealed that sinusoidal endothelial cells are the target of toxic injury related to PAs (25). Recent studies have proved that several PAs-containing medical herbs can cause HSOS (11). According to a study performed in the United States in 1990s, 34% of respondents used unconventional therapy and 3% used herbal medicines (11), which calls out for attention on potential herbal medicine related health problems. In current series, all patients consumed *Gynura segetum* (Tusanqi), a kind of PAs-containing herbal medicine widely used in China and some Asian countries. Most of these patients used *Gynura segetum* root soaked in wine to relieve back and leg pain or treat traumatic injury. Literatures on *Gynura segetum* induced HSOS have been increasingly published recently (9-11). Contrary to the previous sporadic case reports, our study is based on the first sizable cohort.

Hepatic sinusoidal obstruction syndrome is associated with considerable mortality due to the severity of the disease and the absence of effective therapy (11). The overall mortality from HSOS varies from 3% to 67% in different series (26, 27). Supportive and symptomatic care to maintain intravascular volume and renal perfusion without extravascular fluid accumulation is critical (6). Successful management of HSOS depends on early intervention; in our experience, the specific imaging presentation usually evokes the diagnosis for radiologist and clinician.

Ascites, usually accompanied with pleural effusion, is one of the most frequent radiologic presentations in HSOS. Our study showed that ascites can be refractory while the volume of ascites was stable or even progressed in 4 out of 5 follow-up cases. Patchy liver enhancement, equally well demonstrated on both contrast CT and MRI, was also present in all cases. This sign may be the most important imaging feature and usually leads the radiologist to consider HSOS, since it was rare in other liver disorders based on our experience. Pathologically, subintimal thickening could be observed and would lead to venular narrowing and increased resistance to blood flow (6). Then, the part of liver where sinusoidal obstruction or veno-occlusion occurred may show relatively lower enhancement on contrast CT or MRI, which may form the patchy liver enhancement sign. In present study, we found a significant association between radiologic and clinical classification; the extent of abnormal patchy liver enhancement may partly indicate the severity of the disease and help optimize the treatments for patients.

Hepatomegaly was the second most frequent finding; while it was non-specific and may also be the consequence of hypoalbuminemia, it could be observed in patients with infectious hepatitis, or graft-versus-host disease (15). Main hepatic vein narrowing is another important sign favoring the diagnosis of HSOS. In a previous CT based study, investigators found a significantly smaller right hepatic vein diameter in patients with HSOS compared to patients with graft-versus-host disease. They argued that the right hepatic vein measuring less than 4.5 mm in diameter was highly suggestive of HSOS (28). van den Bosch and van Hoe (15), in an imaging case report of two patients with HSOS following stem cell transplantation, described the hepatic vein as narrow but patent. In our study, the right hepatic veins in 10 cases were visualized and measured less than 1.5 mm. For the remaining 6 cases, the hepatic veins were non-measurable in sectional post-contrast images or even multiplanar reformatted images. Given that the primary site of the injury is sinusoidal endothelial cells, the result suggests that these subjects seemed to be the severe cases or in late stage of the disease.

In 4 cases, we noticed that liver parenchyma surrounding the main hepatic veins demonstrated relatively normal enhancement compared to the rest of the patchy enhanced area of liver. This interesting "clover sign" may indicate that the venules adjacent to the main hepatic vein are more likely to keep patent. The lack of pathological evidence calls out for further investigation of the mechanism of this sign. Gallbladder wall thickening and periportal cuffing were observed in 14 cases (87.5%, 14/16) and 6 cases (75%, 6/8), respectively. These two signs are most likely caused by increased resistance to venous inflow and also indicate the primary vascular nature of HSOS (15).

Confounding diagnoses that are relatively common include chloestatic jaundice due to sepsis, drug-induced cholestasis, fluid overload due to renal or heart failure, and liver involvement by fungal or viral infections. In particular, distinguishing between HSOS and Budd-Chiari syndrome remains a big challenge. The clinical manifestations and liver histology in HSOS and Budd-Chiari syndrome are similar to each other due to the common underlying mechanism of hepatic injury and adaptation in response to increased sinusoidal pressure. Thus, the differential diagnosis largely depends on imaging studies. As hepatomegaly, ascites, and even patchy enhancement may also occur in Budd-Chiari syndrome, careful assessment of hepatic veins and inferior

vena cava is crucial to distinguishing these two settings. For PAs-related HSOS, detailed history is another important clue to preclude Budd-Chiari syndrome due to the absence of any herbal medicine induced Budd-Chiari syndrome reported in published literature till now, at least to our knowledge.

In current study, we assessed HSOS based on routine CT and MRI, while some emerging techniques may also be used to detect or evaluate this disease. Ward et al. (29) found that HSOS in patients with treated colorectal metastases could be effectively detected on superparamagnetic iron oxide-enhanced T2-weighted gradient echo images. In a recent study, Shin et al. (30) reported that gadoxetic acid-enhanced magnetic resonance imaging was highly specific for the diagnosis of HSOS in patients with treated colorectal hepatic metastases.

There are three limitations to this study. First, we were unable to perform liver biopsy due to thrombocytopenia, clotting abnormalities and extensive ascites. Therefore, histological evidence has not been available except for one case that accepted liver transplantation. Nonetheless, firm diagnosis was established by strict clinical criteria and definite history of PAs-containing *Gynura segetum* exposure. On the other hand, liver biopsy is also unreliable and may cause false negative due to the patchy nature of HSOS. Second, as a retrospective study, the schedule of imaging examination was not standardized, which may cause individual cases to be scanned at different stages of the disease development. Finally, our study population was relatively small due to the rarity of the disease.

In conclusion, this study first described the characteristics of CT and MRI in PAs-containing herbal medicine induced HSOS. Ascites, patchy liver enhancement, and main hepatic vein narrowing were the most frequent imaging features. The extent of patchy liver enhancement was significantly associated with the clinical severity of the disease. Furthermore, despite the absence of HSOS patient caused by stem cell transplantation or chemotherapy in our study, analogous pathogenesis suggests that the imaging changes may be similar in different HSOS setting irrespective of the cause of disease (11, 15). Thus, the imaging changes in HSOS induced by herbal medicine may be equally helpful for favoring diagnosis of stem cell transplantation related HSOS.

REFERENCES

1. Helmy A. Review article: updates in the pathogenesis and therapy of hepatic sinusoidal obstruction syndrome. *Aliment Pharmacol Ther* 2006;23:11-25
2. Wilmont FC, Robertson GW. Senecio disease, or cirrhosis of the liver due to senecio poisoning. *Lancet* 1920;196:848-849
3. Zuckerman M, Steenkamp V, Stewart MJ. Hepatic veno-occlusive disease as a result of a traditional remedy: confirmation of toxic pyrrolizidine alkaloids as the cause, using an in vitro technique. *J Clin Pathol* 2002;55:676-679
4. Kakar F, Akbarian Z, Leslie T, Mustafa ML, Watson J, van Egmond HP, et al. An outbreak of hepatic veno-occlusive disease in Western afghanistan associated with exposure to wheat flour contaminated with pyrrolizidine alkaloids. *J Toxicol* 2010;2010:313280
5. Ortiz Cansado A, Crespo Valadés E, Morales Blanco P, Sáenz de Santamaría J, González Campillejo JM, Ruiz Téllez T. [Veno-occlusive liver disease due to intake of Senecio vulgaris tea]. *Gastroenterol Hepatol* 1995;18:413-416
6. Kumar S, DeLeve LD, Kamath PS, Tefferi A. Hepatic veno-occlusive disease (sinusoidal obstruction syndrome) after hematopoietic stem cell transplantation. *Mayo Clin Proc* 2003;78:589-598
7. Alpert LI. Veno-occlusive disease of the liver associated with oral contraceptives: case report and review of literature. *Hum Pathol* 1976;7:709-718
8. Fajardo LF, Colby TV. Pathogenesis of veno-occlusive liver disease after radiation. *Arch Pathol Lab Med* 1980;104:584-588
9. Lin G, Wang JY, Li N, Li M, Gao H, Ji Y, et al. Hepatic sinusoidal obstruction syndrome associated with consumption of Gynura segetum. *J Hepatol* 2011;54:666-673
10. Dai HF, Gao Y, Yang M, Yu CH, Gu ZY, Chen WX. Hepatic veno-occlusive disease induced by Gymura segetum: report of two cases. *Hepatobiliary Pancreat Dis Int* 2006;5:406-408
11. Chen Z, Huo JR. Hepatic veno-occlusive disease associated with toxicity of pyrrolizidine alkaloids in herbal preparations. *Neth J Med* 2010;68:252-260
12. Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, et al. Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation* 1987;44:778-783
13. McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology* 1984;4:116-122
14. Wu XW, Wang WQ, Liu B, Xu JM, Yu YQ, Zhang S, et al. Hepatic veno-occlusive disease after taking Gynura Rhizome: the value of multidetector computed tomography in diagnosing the disease and evaluating the clinical therapeutic effect. *Hepatol Res* 2012;42:304-309
15. van den Bosch MA, van Hoe L. MR imaging findings in two patients with hepatic veno-occlusive disease following bone

marrow transplantation. *Eur Radiol* 2000;10:1290-1293
16. Dumont Ch, Lambert M, Van Beers BE. MR imaging findings in a patient with hepatic veno-occlusive disease. *Acta Gastroenterol Belg* 2004;67:236-238
17. Mortelé KJ, Van Vlierberghe H, Wiesner W, Ros PR. Hepatic veno-occlusive disease: MRI findings. *Abdom Imaging* 2002;27:523-526
18. Gao H, Li N, Wang JY, Zhang SC, Lin G. Definitive diagnosis of hepatic sinusoidal obstruction syndrome induced by pyrrolizidine alkaloids. *J Dig Dis* 2012;13:33-39
19. DeLeve LD, Valla DC, Garcia-Tsao G. Vascular disorders of the liver. *Hepatology* 2009;49:1729-1764
20. Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993;46:1323-1330
21. McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med* 1993;118:255-267
22. Mahgerefteh SY, Sosna J, Bogot N, Shapira MY, Pappo O, Bloom AI. Radiologic imaging and intervention for gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *Radiology* 2011;258:660-671
23. Gray H, Williams PL, Bannister LH. *Gray's anatomy: the anatomical basis of medicine and surgery*, 38th ed. New York: Churchill Livingstone, 1995:1902-1903
24. Sharma D, Deshmukh A, Raina VK. Surgical anatomy of retrohepatic inferior vena cava and hepatic veins: a quantitative assessment. *Indian J Gastroenterol* 2001;20:136-139
25. DeLeve LD, McCuskey RS, Wang X, Hu L, McCuskey MK, Epstein RB, et al. Characterization of a reproducible rat model of hepatic veno-occlusive disease. *Hepatology* 1999;29:1779-1791
26. Méresse V, Hartmann O, Vassal G, Benhamou E, Valteau-Couanet D, Brugieres L, et al. Risk factors for hepatic veno-occlusive disease after high-dose busulfan-containing regimens followed by autologous bone marrow transplantation: a study in 136 children. *Bone Marrow Transplant* 1992;10:135-141
27. Ayash LJ, Hunt M, Antman K, Nadler L, Wheeler C, Takvorian T, et al. Hepatic venoocclusive disease in autologous bone marrow transplantation of solid tumors and lymphomas. *J Clin Oncol* 1990;8:1699-1706
28. Erturk SM, Mortelé KJ, Binkert CA, Glickman JN, Oliva MR, Ros PR, et al. CT features of hepatic venoocclusive disease and hepatic graft-versus-host disease in patients after hematopoietic stem cell transplantation. *AJR Am J Roentgenol* 2006;186:1497-1501
29. Ward J, Guthrie JA, Sheridan MB, Boyes S, Smith JT, Wilson D, et al. Sinusoidal obstructive syndrome diagnosed with superparamagnetic iron oxide-enhanced magnetic resonance imaging in patients with chemotherapy-treated colorectal liver metastases. *J Clin Oncol* 2008;26:4304-4310
30. Shin NY, Kim MJ, Lim JS, Park MS, Chung YE, Choi JY, et al. Accuracy of gadoxetic acid-enhanced magnetic resonance imaging for the diagnosis of sinusoidal obstruction syndrome in patients with chemotherapy-treated colorectal liver metastases. *Eur Radiol* 2012;22:864-871