Acoustic Radiation Force Impulse Elastography and Contrast-Enhanced Sonography of Sinusoidal Obstructive Syndrome (Veno-occlusive Disease)

Preliminary Results

Teresa Fontanilla, MD, Concepción González Hernando, MD, Juan Cristóbal Valenzuela Claros, MD, Guiomar Bautista, MD, Javier Minaya, MD, Maria del Carmen Vega, MD, Ana Piazza, MD, Santiago Méndez, MD, Claudio Rodriguez, MD, Rafael Pérez Arangüena, MD

We report quantitative liver acoustic radiation force impulse (ARFI) elastographic findings in 2 cases of sinusoidal obstructive syndrome and liver contrast-enhanced sonographic features in one of these cases. To our knowledge, findings in this condition from these techniques have not been reported previously. Acoustic radiation force impulse elastography showed median high shear wave velocities (case 1, 2.75 m/s; case 2, 2.58 m/s) that normalized after specific treatment for sinusoidal obstructive syndrome; therefore, ARFI elastography provided quantitative information that helped diagnose this condition as well as monitor the response to treatment. Contrast-enhanced sonographic findings in one of the cases showed patchy liver enhancement that correlated with the high-velocity patchy distribution on ARFI elastography in that case and enhanced multidetector row computed tomographic findings in the other case. This contrast-enhanced sonographic pattern progressively normalized during follow-up after specific treatment. The elastographic features in both cases and contrast-enhanced sonographic features in one of them contributed to early diagnosis and follow-up of sinusoidal obstructive syndrome in both patients. Further prospective studies are necessary to define the role of ARFI elastography and contrast-enhanced sonography in the early diagnosis and clinical follow-up of this condition.

Key Words—acoustic radiation force impulse elastography; contrast-enhanced sonography; sinusoidal obstructive syndrome; veno-occlusive disease

This series describes 2 patients whose early and accurate diagnosis of sinusoidal obstructive syndrome may have been responsible for their good clinical courses. The aim of this article is to report the acoustic radiation force (ARFI) impulse elastographic findings in both patients and the contrast-enhanced sonographic findings in one of these patients. To our knowledge, there are no previous reports on the ARFI elastographic or contrast-enhanced sonographic features in this disease. Clinical data, B-mode findings, and spectral and color Doppler findings in both cases and multidetector row computed tomographic (CT) findings in one of them also contributed to the diagnosis.
Case Descriptions

Case 1
This patient was a 46-year-old woman with follicular-type non-Hodgkin lymphoma. One month after beginning treatment with a second cycle of monoclonal antibodies, signs and symptoms of sinusoidal obstructive syndrome or Budd-Chiari syndrome developed.

Contrast-enhanced CT was first performed with a 64-multidetector row system (Somatom Sensation 64; Siemens Medical Solutions, Malvern, PA) and revealed delayed and patchy liver parenchymal enhancement but was unable to show patency of the hepatic veins, so the possibility of Budd-Chiari syndrome was raised (Figure 1). B-mode and Doppler sonography revealed hepatomegaly, free peritoneal fluid, biliary and bladder wall thickening, narrowed but patent hepatic veins with monophasic flow toward the heart (ruling out Budd-Chiari syndrome), and

Figure 1. Case 1: sinusoidal obstructive syndrome in a 46-year-old woman with follicular-type non-Hodgkin lymphoma. A, Arterial phase contrast-enhanced multidetector row computed tomogram showing delayed liver enhancement in comparison with the spleen. The inferior vena cava (arrow) is compressed. Hepatic veins are not shown. Ascites and pleural effusion are also depicted. B, Portal venous phase computed tomogram showing patchy liver enhancement with a geographic pattern. Patent hepatic veins are not shown, raising the possibility of acute Budd-Chiari syndrome. C, Gray scale sonogram showing a homogeneous liver and a very narrowed (compressed) inferior vena cava (white arrow) and middle hepatic vein (black arrow). D, Color Doppler sonogram showing hepatic vein patency; spectral Doppler imaging shows that the flow direction is correct, toward the heart, but the spectrum morphologic pattern is monophasic, which in the absence of chronic hepatic disease signs suggests liver congestion.

(continued)
a slightly diminished portal vein velocity (14 cm/s). Acoustic radiation force impulse elastography was performed with an Acuson S2000 system (Siemens Medical Solutions, Mountain View, CA) and a convex 4-MHz multifrequency probe after the B-mode and Doppler explorations during the same radiologic session. This probe makes it possible to measure liver stiffness in a region of interest with a maximum depth of 5.5 cm. Ten measurements of the right hepatic lobe were performed with an intercostal approach, as recommended by the manufacturer and the literature, and were registered in a table; this procedure took about 3 minutes. Acoustic radiation force impulse elastography of the right hepatic lobe showed very high velocities with a median value of 2.75 m/s (velocities higher than the cutoff value of 1.2 m/s were considered abnormal). Informed consent for all procedures was obtained.

Considering all of the findings, sinusoidal obstructive syndrome was suggested and was confirmed by histologic analysis after transjugular biopsy. Sonographic and elastographic follow-up 2 months after treatment showed normal Doppler and elastographic values: a portal vein velocity of 23 cm/s and an elastographic median velocity of 1.2 m/s.

**Case 2**

This patient was a 51-year-old woman with allogeneic stem cell transplantation for acute lymphoblastic leukemia. Signs and symptoms of sinusoidal obstructive syndrome disease appeared on day 44 after the transplantation. B-mode sonography revealed ascites, some subtle hypoechoic parenchymal areas, normal portal velocity, and otherwise normal findings. Acoustic radiation force impulse elastography (performed the same way as in case 1) showed very high velocities with a median velocity of 2.58 m/s, suggestive of hepatic impairment. Interestingly, the shear velocity was higher in the hypoechoic areas than in the rest of the parenchyma (Figure 2). Contrast-enhanced sonography was performed with the same machine and probe and specific contrast technology (Cadence contrast pulse sequencing) after intravenous bolus administration of 2.4 mL of a sulfur hexafluoride–based contrast agent (SonoVue; Bracco SpA, Milan, Italy) flushed with a 10-mL saline bolus. This technique includes a low mechanical index to minimize microbubble rupture and suppresses the basal image, which makes the technique exquisitely sensitive to microvascular enhancement. Contrast-enhanced sonography revealed patchy enhancement during all phases, with a geographic morphologic pattern best depicted during the portal phase. The less enhanced areas corresponded to the areas with the highest shear wave velocities on ARFI elastography. Time-intensity contrast uptake curves were obtained during the first 30 seconds after contrast agent injection, comparing hypoenhanced and normally enhanced areas. Diminished areas under the curves were seen in the curves obtained in the less enhanced areas. Informed consent for all procedures was obtained.

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**Figure 1.** (continued) **E**, Color Doppler sonogram showing hepatopetal but slightly diminished portal flow (velocity, 14 cm/s). Follow-up (not shown) showed a velocity of 23 cm/s. **F**, Acoustic radiation force impulse elastography image showing a pathologic shear wave velocity of 2.5 m/s, which in the absence of a history and signs of chronic liver disease suggests hepatic congestion.
Clinical improvement after specific treatment and progressive normalization of the patchy liver contrast enhancement pattern and elastographic values during follow-up were considered confirmation of sinusoidal obstructive syndrome.

Discussion

Sinusoidal obstructive syndrome, also known as hepatic veno-occlusive disease, is a well-recognized complication of hematopoietic stem cell transplantation that may also be related to high-dose chemotherapy for malignancy and has been described after monoclonal antibody treatment. It is related to the pretransplantation conditioning regimen for stem cell transplantation or to high-dose chemotherapy. The underlying mechanism of injury is toxic endothelial damage of the hepatic sinusoids that leads to obstruction of sinusoidal and postsinusoidal venous outflow. This congestive state may eventually produce alterations in portal venous flow and portal hypertension. There is also evidence of hepatocyte injury and death, with a centrilobular distribution.

Figure 2. Case 2: sinusoidal obstructive syndrome in a 51-year-old woman with allogenic stem cell transplantation for acute lymphoblastic leukemia. A, Transverse gray scale sonogram of the right liver lobe showing a slightly hypoechoic area (arrows). Acoustic radiation force impulse elastography of the normal-appearing parenchyma shows a high shear wave velocity of 2.40 m/s. B, Elastographic region of interest now in the hypoechoic area (arrows) and showing a very high shear wave velocity (4.31 m/s), indicating that the condition affects the liver parenchyma in a heterogeneous fashion. C, Contrast-enhanced sonogram 56 seconds after injection of the contrast agent showing patchy geographic areas of hypoenhancement (black arrows). Free peritoneal fluid (white arrow) is also shown. This pattern persisted throughout all of the enhancement phases. D, Contrast agent uptake time-intensity curves obtained during the arterial phase. Curves 3 and 4 show diminished enhancement (corresponding to the hypoenhanced areas) compared to curves 1 and 2 (corresponding to the normally enhanced areas).
Sinusoidal obstructive syndrome is usually diagnosed on the basis of 2 clinical criteria proposed by the Baltimore and Seattle groups. The clinical criteria for defining sinusoidal obstructive syndrome include painful hepatomegaly, jaundice, hyperbilirubinemia, ascites, and unexplained weight gain, but recognition of this disease can be challenging because other conditions may have similar manifestations. These conditions include acute hepatic graft-versus-host disease, cholestatic disorders, and infections, among others.

Sonographic features vary and are related to the degree of hepatic congestion and to the increased resistance to portal venous inflow. Gray scale findings include ascites, biliary and bladder wall thickening, hepatomegaly, and hepatic vein narrowing. Portal Doppler sonography reflects the severity of the condition. At first, portal venous flow is spared, but as the hepatic involvement worsens, portal flow demodulation occurs; then the portal velocity diminishes; and eventually, reversed flow ensues. The arterial resistive index usually increases as well, although controversy exists over whether measurement of the hepatic artery resistive index is valuable for diagnosis and clinical follow-up of sinusoidal obstructive syndrome. The resistive index was not measured in our patients. Loss of triphasic hepatic venous outflow (as in our cases) is usually present, due to the loss of hepatic compliance. It has been reported by Lassau et al that detection of ascites, gallbladder wall thickening, and reversed portal venous flow is valid for the diagnosis of sinusoidal obstructive syndrome, and the American Association for the Study of Liver Diseases recommends the use of gray scale and Doppler sonography to aid in the diagnosis of this condition. The problem is that gray scale findings are nonspecific, and reversed portal flow ensues late in the disease. As a matter of fact, in one of our cases, the portal velocity was normal, and in the other, it was minimally diminished. Subtle and progressive portal velocity reduction is difficult to assess if there is no previous basal Doppler sonographic examination, as in our cases. Sinusoidal obstructive syndrome contributes to hepatomegaly in stem cell transplant recipients and oncologic patients; therefore, development of new modalities for its early diagnosis is an important task.

The finding of patchy liver enhancement on multidetector row CT (case 1) and contrast-enhanced sonography (case 2) further suggested sinusoidal obstructive syndrome. Patchy liver enhancement in sinusoidal obstructive syndrome has been reported on CT and magnetic resonance imaging but to our knowledge, contrast-enhanced sonographic findings in sinusoidal obstructive syndrome have not been reported previously. The contrast-enhanced sonographic findings are coincident with those described for magnetic resonance imaging and CT and reflect the hepatic hemodynamic changes and the state of congestion. The patchy enhancement seen on contrast-enhanced sonography in case 2 and on multidetector row CT in case 1 presumably is determined by differences in the severity of the involvement in different areas. A time-intensity curve comparison provided quantitative data that confirmed the qualitative imaging findings of diminished enhancement in some areas. Contrast-enhanced sonographic follow-up at 1 month in case 2 revealed homogeneous enhancement that was coincidental with the clinical improvement. The patchy enhancement on contrast-enhanced sonography might be quite specific for the diagnosis of sinusoidal obstructive syndrome. Other theoretical causes of patchy enhancement include hemodynamic alterations in chronic hepatic disease (not present in these cases), Budd-Chiari syndrome, and heart failure.

As yet, there are no reports of parenchymal enhancement on contrast-enhanced sonography in Budd-Chiari syndrome. A differential diagnosis with acute Budd-Chiari syndrome on multidetector row CT may be difficult if the hepatic veins are compressed due to hepatic congestion (case 1) because patchy enhancement is present as well. Typically, Budd-Chiari syndrome shows patchy decreased peripheral enhancement and stronger enhancement of the central portion of the liver parenchyma (caudate lobe and pericava) with gradual extension to the peripheral areas after a time delay. However, a mosaic heterogeneous perfusion pattern diffusely involving the liver may be seen, and enhancement patterns will depend on the relative degree of obstruction of the various draining veins. Doppler sonography is able to show hepatic vein and inferior vena cava permeability and to exclude Budd-Chiari syndrome, as in our case 1. Congestive cardiac failure may also show heterogeneous liver enhancement on multidetector row CT, but the pattern is a mottled mosaic, and the hepatic veins are distended instead of narrowed. Contrast-enhanced sonography of hemodynamic disorders, including sinusoidal obstructive syndrome, is an area for future study.

Acoustic radiation force impulse elastography is a tissue strain imaging technique that uses sound waves to interrogate the mechanical stiffness properties of tissues and provides quantitative information about shear wave propagation. The shear wave velocity is directly related to the tissue elasticity: the stiffer the liver, the higher the speed. This technique has a maximum depth of 5.5 cm, which may be a limitation in very obese patients or in the presence of substantial ascites, but it was not a problem in our cases.

Acoustic radiation force impulse elastography has proved to have high performance for diagnosing and stag-
ing liver fibrosis in chronic hepatitis C and is useful in nonalcoholic fatty liver.17 We have also found pathologic ARFI elastographic velocities in other clinical scenarios, such as congestive heart failure, acute viral hepatitis, acute graft rejection in hepatic transplantation, and lupus hepatitis, among others. Reports of ARFI elastography in these situations, however, are scarce, although transient elastographic findings in congestive heart failure have been reported.18 That study showed that liver stiffness is increased in patients with clinical signs of acute decompensated heart failure, and clinical compensation leads to a decrease in liver stiffness. Indeed, high values on ARFI elastography are not specific for fibrosis, and in our experience, they may be normalized if the acute condition is reversed. Although they were nonspecific, the very high velocities on ARFI elastography helped determine the presence of severe hepatic impairment in both of our cases, even though the basal echogenicity was homogeneous in case 1. The fact that the velocities were higher in some areas probably reflected more severe involvement in these areas. Moreover, these areas were coincidental with the less enhanced areas on contrast-enhanced sonography. The improvement in the elastographic shear wave velocities after treatment in both cases served to confirm resolution of the condition. Therefore, ARFI elastography might have a potential role in the follow-up of sinusoidal obstructive syndrome.

We think that patients undergoing stem cell transplantation and chemotherapy and monoclonal antibody regimens related to sinusoidal obstructive syndrome could benefit from initial ARFI elastography and Doppler sonography with measurement of the portal velocity, which would provide baseline morphologic, elastographic, and hemodynamic information for comparison in the event that sinusoidal obstructive syndrome is suspected. In such cases, contrast-enhanced sonography is also recommended.

In conclusion, two new sonographic tools, ARFI elastography and contrast-enhanced sonography, improved the performance of sonography and helped make an accurate and early diagnosis of sinusoidal obstructive syndrome in both of our cases. Our findings suggest that these techniques may be useful tools for clinical follow-up of sinusoidal obstructive syndrome. Further prospective studies are necessary to define the role of ARFI elastography and contrast-enhanced sonography in the early diagnosis and clinical follow-up of sinusoidal obstructive syndrome.

References