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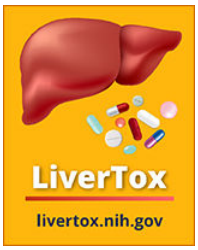
**NLM Citation:** LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Sinusoidal Obstruction Syndrome (Veno-occlusive Disease). [Updated 2019 May 4].
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/




# Sinusoidal Obstruction Syndrome (Veno-occlusive Disease)

Updated: May 4, 2019.

**Definition**. Sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease (VOD), is a distinctive and potentially fatal form of hepatic injury that occurs predominantly, if not only, after drug or toxin exposure. SOS can present in an acute, subacute or chronic form usually with abdominal pain and swelling, with evidence of portal hypertension and variable degrees of serum enzyme elevations and jaundice. Liver histology demonstrates obstruction of sinusoids in central areas with hepatocyte necrosis and hemorrhage.

**Latency to Onset**. The acute form of SOS presents within 1 to 3 weeks of exposure to the medication (which can be a single infusion). The subacute and chronic forms of SOS present weeks, months or even years after starting.

**Symptoms**. Acute SOS typically presents with abdominal pain and swelling, weight gain and signs of portal hypertension (ascites, edema, varices). Jaundice is generally mild or absent initially, but may develop and worsen if the injury is severe. The subacute and chronic forms of SOS typically present with fatigue and abdominal swelling with signs and symptoms of portal hypertension including edema, ascites, varices, hepatic encephalopathy or muscle wasting and weakness.

**Serum Enzyme Elevations.** Acute SOS can present with a hepatocellular pattern of serum enzyme elevations with marked increases in ALT and AST (>10 times ULN) and mild or minimal increases in alkaline phosphatase. However, in some situations, serum enzymes are minimally or not elevated and patients present with ascites, fluid overload, signs of hepatic failure and progressive jaundice. In chronic SOS, serum enzymes are modestly elevated and are either hepatocellular or mixed.

**Drugs**. Agents that cause SOS include cancer chemotherapeutic agents, particularly the alkylating agents such as busulfan, cyclophosphamide, melphalan, carmustine (BCNU), thiotepa, dacarbazine, and the platinum coordination complexes - carboplatin, cisplatin and oxaliplatin. The thiopurines, such as azathioprine, mercaptopurine and thioguanine, have also been implicated in rare cases of SOS, usually when given in high doses in combination with other agents. Finally, the pyrrolizidine alkaloids which are found in many plants and shrubs are well known causes of SOS, this exposure being linked usually to bush tea, and instances of contamination of food sources such as rice or wheat with pyrrolizidine containing weeds or plants.

**Differential Diagnosis**. The diagnosis of SOS usually rests on a typical clinical presentation and exclusion of other causes of liver injury. In the setting of bone marrow transplantation [currently referred to as hematopoietic cell transplantation], the usual differential diagnosis includes graft-vs-host disease, sepsis, other forms of drug induced liver injury and unusual forms of viral hepatitis (herpes simplex). The diagnosis is usually supported by imaging demonstrating changes typical of sinusoidal obstruction. Liver biopsy is diagnostic but not usually needed and difficult because of concurrent coagulopathy or thrombocytopenia.

**Clinical Features and Outcome**. Sinusoidal obstruction syndrome can be classified as acute, subacute or chronic in presentation. Acute presentation is typically with sudden onset of hepatomegaly, abdominal pain, fluid retention, jaundice and ascites. Serum aminotransferase levels are usually high, with minimal increase in

alkaline phosphatase. The peak of ALT elevations occur days or weeks after initial presentation. This syndrome is fatal in 20% to 50% of patients with SOS, due to high dose chemotherapy or chemoradiation regimens used in preparation of hematopoietic cell transplantation. In nonfatal cases, recovery usually proceeds over 50 to 100 days. The rapid onset of weight gain and jaundice, extreme elevations in serum ALT levels and presence of renal or respiratory failure are poor prognostic signs.

Subacute and chronic veno-occlusive disease usually occurs with chronic low dose ingestion of pyrrolizidine alkaloids or oral chemotherapeutic agents (such as thioguanine). Patients present with the insidious onset of fatigue, abdominal distension and signs and symptoms of portal hypertension. Cirrhosis may be present at the time of clinical presentation.

The clinical features and course of sinusoidal obstruction syndrome has been most clearly defined in the setting of hematopoietic cell transplantation after conditioning with cytotoxic agents or chemoradiation. The onset of sinusoidal obstruction syndrome is typically within 10 to 20 days after transplantation. However, with less aggressive regimens and cancer chemotherapy it can arise as much as 3 to 6 weeks after starting therapy. The typical presentation is onset of unexplained weight gain within a week of transplantation, followed by abdominal or right upper quadrant pain and tenderness, abdominal distention due to ascites, and jaundice. Depending upon the severity of the injury, the onset can be abrupt and associated with sudden onset of severe abdominal pain and rapid progression to hepatic and multiorgan failure or be more insidious with appearance of tender hepatomegaly, mild weight gain and serum enzyme elevations with mild or minimal jaundice. The clinical syndrome is similar to Budd Chiari syndrome (hepatic vein thrombosis), but the obstruction is due to narrowing and occlusion of sinusoids and small hepatic venules rather than thrombosis of the larger hepatic veins. At least 80% of patients with sinusoidal obstruction syndrome recover.

The most common form of SOS is a complication of cancer chemotherapy and is typically found after use of high doses of alkylating agents (busulfan, cyclophosphamide, melphalan, carmustine) and total body irradiation, most commonly when they are used in combination myeloablative regimens in preparation for hematopoietic cell transplantation. These regimens are meant to cause toxic cell death to malignant hematopoetic cells as well as ablate the host immune system to allow for engraftment of an allogenic hematopoietic cells. The high doses used, however, can also injure normal cells, the sinusoidal endothelial cells being particularly vulnerable. SOS can also occur after administration of single chemotherapeutic agents in nonmyeloablative doses, such as with cyclic intravenous infusions of dacarbazine (DTIC), gemtuzumab (a toxin conjugated anti-CD33 monoclonal antibody), oxaliplatin and carboplatin and, rarely, other single chemotherapy drugs. Chronic administration of the antimetabolites 6-thioguanine, azathioprine and mercaptopurine can also cause SOS, although the presentation is typically subacute or chronic.

**Diagnosis**. After cancer chemotherapy or conditioning for hematopoietic cell transplantation, SOS can often be diagnosed based upon clinical symptoms, signs and routine laboratory tests. Liver histology is diagnostic but not always practicable, because of the thrombocytopenia and neutropenia present after chemotherapy or myeloablation. Transjugular liver biopsy and concurrent measurement of the hepatic venous pressure gradient is perhaps the most reliable means of diagnosis and grading for severity (based upon the presence and degree of portal hypertension).

In clinical situations, SOS is usually diagnosed using established criteria of liver injury arising within 20 days of bone marrow transplantation with at least two of the following: (1) rise of serum bilirubin above 2.0 mg/dL, (2) hepatomegaly and/or tenderness or pain over the liver, and (3) sudden weight gain (>2% of body weight) attributable to fluid accumulation. Other possible diagnoses in this situation include graft-vs-host disease, septicemia, viral hepatitis, heart failure or tumor infiltration of the liver, all of which can usually be excluded by clinical, biochemical or radiological features. Prospective application of these criteria has been found to be 85% to 95% sensitive and similarly specific for this diagnosis. Some regimens have resulted in a delayed appearance of SOS after myeloablation (20 to 35 days), and the syndrome can arise after a second, third or later cycle of

chemotherapy. Furthermore, the routine use of ursodiol as prophylaxis against SOS appears to be associated with lesser degrees of jaundice and perhaps a milder course of illness. Ultrasound examination of the liver can suggest this diagnosis by demonstrating hepatomegaly, ascites and changes in liver texture suggestive of congestion. In addition, ultrasound can help to exclude acute Budd Chiari syndrome and portal vein thrombosis by the demonstration of patency of large hepatic and portal veins. Doppler ultrasound can demonstrate evidence of portal hypertension, alterations in both portal and hepatic vein flow, and impedance to hepatic artery blood flow. Measurement of the hepatic venous pressure gradient can also demonstrate portal hypertension which may have prognostic value. The reliability of hepatic elastography in assessing SOS deserves prospective analysis.

**Mechanisms of Injury**. The mechanism of injury in sinusoidal obstruction syndrome is believed to be damage to endothelial cells in the liver followed by their necrosis (apoptosis) and extrusion into sinusoids, leading to obstruction and congestion. Stellate cells become activated and produce extracellular matrix and collagens. Hepatocellular necrosis is probably due to loss of endothelial function, congestion and perhaps direct toxicity of the implicated agents as well. SOS can be produced in animal models, particularly with modulation of glutathione status. The frequency and severity of SOS is at least partially related to drug dosage and pharmacokinetics. Irradiation of the liver can also cause SOS and acts synergistically with antineoplastic agents in causing this syndrome.

**Management**. The first and most important element in management is to avoid further injury and provide support for complications such as hypotension, electrolyte and acid-base imbalance, renal and pulmonary failure and infectious complications. Anticoagulants have been used based upon the possibility of venous thrombosis, but evidence for benefit is lacking and anticoagulation adds unnecessary complexity of the clinical situation. Infusions of n-acetyl cysteine to replenish glutathione levels may be beneficial as this approach is protective in animal models and is effective in other forms of acute liver failure. Defibrotide, a mixture of porcine oligodeoxyribonucletides with antithrombotic and profibrinolytic features, has been used with promising evidence of benefit. Liver transplantation is rarely indicated in the setting of advanced malignancy and myeloablation.

Prevention of SOS is more likely to be effective than application of therapies after the injury has occurred. Most important is the assessment of the likelihood of SOS and use of chemotherapies and conditioning regimens with lower rates of this complication in patients at highest risk (preexisting liver disease, previous myeloablative therapies and prior liver irradiation). Repletion of glutathione by n-acetyl cysteine or other means may be a reasonable approach to decreasing the rate of SOS after cytotoxic therapy and myeloablation, but glutathione repletion may also decrease the efficacy of the chemotherapy for malignancies. As long as more aggressive cytotoxic therapies are used for advanced cancer, SOS will continue to be a problematic complication. In recent years, the frequency of sinusoidal obstruction syndrome has fallen markedly partially because of the use of less aggressive myeloablative regimens, monitoring of drug levels, appropriate use of pharmacokinetic information and a decrease in chronic hepatitis C among bone marrow recipients, the consequence of introduction of screening of donor blood for anti-HCV and decrease in posttransfusion hepatitis C.

# Representative Cases

## Case 1. Acute veno-occlusive disease and liver failure due to dacarbazine.

[Modified from: Ceci G, Bella M, Melissari M, Gabrielli M, Bocchi P, Cocconi G. Fatal hepatic toxicity of DTIC: Is it really a rare event? Cancer 1985; 61: 1988-91. PubMed Citation]

A 52 year old man with metastatic malignant melanoma developed fever during day 2 of a second cycle of dacarbazine, followed on day 4 by acute abdominal pain and shock. He had tolerated the first cycle of dacarbazine with only mild nausea and vomiting and a few days of fever of 38-39 oC immediately after the 5 day

course. At the time of restarting dacarbazine, he was without symptoms and the tumor had decreased in size. On presentation with hepatic injury, he was hypotensive and had tender hepatomegaly. Laboratory tests showed total bilirubin of 2.8 mg/dL, ALT 2050 U/L, AST 2990 U/L, LDH 3270 U/L, alkaline phosphatase 153 U/L, and INR 1.64. Ultrasound of the abdomen showed an enlarged liver and ascites. Acute cholecystitis was suspected and a laparotomy was performed. The gallbladder showed signs of chronic inflammation but no perforation. The liver was enlarged and dark. A liver biopsy showed diffuse centrolobular hepatic necrosis and hemorrhage. After surgery he developed multiorgan failure and progressive hepatic decompensation, dying on hospital day 8. At autopsy, the liver was enlarged and histology showed centrolobular necrosis and hemorrhage with occlusion of small and medium sized hepatic veins.

### Key Points

| | |
|---|---|
| Medication: | Dacarbazine, 250 mg/m2 for 5 days every 3 weeks |
| Pattern: | Hepatocellular (R=~35) |
| Severity: | 5+ (fatal) |
| Latency: | 2 days (fever) |
| Recovery: | None |
| Other medications: | Metoclopramide for nausea |

### Comment

The acute hepatitis injury attributed to dacarbazine has a very typical clinical presentation and course, with evidence of acute hepatic necrosis as shown by a marked early rise in ALT and LDH with coagulopathy that reverses rapidly if not fatal. The fever and nausea associated with the first course of dacarbazine is also typical. While the pathology demonstrates veno-occlusive disease, there also appears to be an element of acute ischemic necrosis. The rapid appearance on reexposure and the frequent occurrence of fever and eosinophilia suggests a hypersensitivity reaction. In this case, the emergency cholecystectomy only complicated the course.

## Case 2. Mild sinusoidal obstruction syndrome after hematopoietic cell transplantation.

[Data provided by Dr. George B. McDonald from the files of the Fred Hutchinson Cancer Center]

A 56 year old woman with myelofibrosis and agnogenic myeloid metaplasia underwent allogeneic hematopoietic cell transplantation after a conditioning regimen of oral busulfan (16 mg/kg with therapeutic drug monitoring), followed by intravenous cyclophosphamide (120 mg/kg) and prophylactic ursodiol therapy. One week later she became jaundiced and had mild hepatic tenderness. She had gained approximately 10% of her initial body weight. Liver enzyme levels did not change and serum creatinine was stable (0.7 to 1.0 mg/dL). She had complications of staphylococcal bacteremia and pulmonary fungal infection and was treated for gastrointestinal graft-vs-host disease, but responded to antibiotic and antifungal therapy and was discharged 28 days after the transplant at which time her weight was back to baseline.

### Key Points

| | |
|---|---|
| Medication: | Busulfan and cyclophosphamide conditioning regimen |
| Pattern: | Normal ALT and alkaline phosphatase levels |
| Severity: | 2+ (mild jaundice not prolonging hospitalization) |
| Latency: | 8 days |
| Recovery: | 3 weeks |

*Table continued from previous page.*

| | |
|---|---|
| Other medications: | Ursodiol |

## Laboratory Values

| Days After Transplant | ALT (U/L) | Alk P (U/L) | Bilirubin (mg/dL) | Other |
|---|---|---|---|---|
| -5 | 13 | 184 | 0.7 | Conditioning |
| 0 | 8 | 187 | 0.6 | Transplant |
| 7 | 10 | 179 | 1.0 | |
| 8 | 10 | 144 | 4.3 | Peak weight gain |
| 9 | 19 | 135 | 3.0 | |
| 10 | 16 | 127 | 2.3 | Pleural effusion |
| 11 | 17 | 109 | 2.0 | |
| 14 | 59 | 108 | 2.0 | GvH disease: prednisone |
| 18 | 21 | 115 | 1.0 | |
| 28 | 17 | 86 | 1.0 | Weight background |
| **Normal** | **<49** | **<121** | **<1.2** | |

## Comment

The only evidence of sinusoidal obstruction syndrome was the appearance of jaundice with mild hepatic tenderness and weight gain within 1 to 2 weeks of a conditioning regimen for hematopoietic cell transplantation. Careful use of conditioning agents, therapeutic drug monitoring and prophylaxis with ursodiol may have been the reason for the lack of serum enzyme elevations and mild course.

# Case 3. Moderate sinusoidal obstruction syndrome after hematopoietic cell transplantation.

[Data provided by Dr. George B. McDonald from the files of the Fred Hutchinson Cancer Center]

A 48 year old woman with agnogenic myeloid metaplasia underwent allogeneic hematopoietic cell transplantation after a conditioning regimen of oral busulfan (16 mg/kg with therapeutic drug monitoring), followed by intravenous cyclophosphamide (120 mg/kg). A pretransplant liver biopsy showed extramedullary hematopoiesis and sinusoidal fibrosis. One week after transplantation, she became jaundiced and had weight gain and hepatic tenderness. Serum enzyme levels did not change appreciably, but serum creatinine rose (from 1.1 pretransplant to 2.6 by day 30). She developed mild ascites and was treated with defibrotide infusions for suspected sinusoidal obstruction syndrome. Serum bilirubin peaked at 14.4 mg/dL on day 25 and then slowly improved (Table). She was discharged home after 80 days with signs of jaundice and mild portal hypertension.

## Key Points

| | |
|---|---|
| Medication: | Busulfan and cyclophosphamide conditioning regimen |
| Pattern: | Minimal or no ALT and alkaline phosphatase elevations |
| Severity: | 4+ (jaundice and ascites) |
| Latency: | 5 days |
| Recovery: | >12 weeks |

### Laboratory Values

| Days After Transplant | ALT (U/L) | Alk P (U/L) | Total Bilirubin (mg/dL) | Other |
|---|---|---|---|---|
| -5 | 4 | 188 | 0.8 | |
| 0 | 44 | 167 | 1.2 | |
| 5 | 27 | 186 | 2.6 | |
| 10 | 5 | 123 | 4.0 | |
| 15 | 9 | 114 | 7.0 | Defibrotide started |
| 20 | 10 | 91 | 10.6 | Creatinine 1.6 mg/dL |
| 25 | 52 | 74 | 14.4 | Enterococcal pneumonia |
| 30 | 25 | 120 | 9.7 | Creatinine 2.6 mg/dL |
| 35 | 11 | 107 | 5.2 | Staphylococcal bacteremia |
| 40 | 11 | 80 | 4.7 | Gastric GvHD by biopsy |
| 50 | 19 | 73 | 5.7 | |
| 60 | 22 | 51 | 3.4 | |
| 70 | 21 | 48 | 4.6 | CMV viremia, GI bleeding |
| 80 | 15 | 52 | 3.6 | Creatinine 1.8 mg/dL |
| **Normal** | **<49** | **<121** | **<1.2** | |

### Comment

This patient had a recognized risk factor for severe SOS - sinusoidal fibrosis related to extramedullary hematopoiesis. The clinical presentation was typical of SOS with weight gain, jaundice and appearance of ascites and pleural effusions. At the time of discharge, the patient was still jaundiced and had manifestations of portal hypertension (ascites). This case was considered moderate in severity because of marked jaundice and need for defibrotide, but without renal failure requiring dialysis or ventilator failure, which are common in severe SOS. This was an early case of SOS and prophylactic ursodiol was not given.

## Hepatic Histology of Sinusoid Obstruction Syndrome

Liver histology in SOS varies depending upon stage of injury. Early there is dilation of sinusoids and extravasation of red blood cells into the space of Disse (Figure 1). Later there is collagen deposition in sinusoids and small hepatic veins with further congestion, centrolobular (zone 3) necrosis and apparent occlusion of hepatic venules. The sinusoidal injury is not usually distinctive on light microscopy, but the venular lesions are pathognomonic. Typically, the vein lumen is narrowed by infiltration of cells and blood between the endothelium and the collagen of the vein wall (Figure 2). The change is best seen on a Masson trichrome stain, where the blue of the preexisting collagen contrasts with the red fibers of newly deposited collagen (Figure 3). The damage is usually not apparent in every acinus and vein, except in severe cases. The degree of hepatocellular necrosis correlates with the height of serum enzyme elevations and time of peak ischemic necrosis. While patients can recover from acute sinusoidal obstruction syndrome, reported long term outcomes include cirrhosis and nodular regeneration, particularly with chronic exposure to toxins or cytotoxic agents.

## Histologic Images

Photomicrographs by

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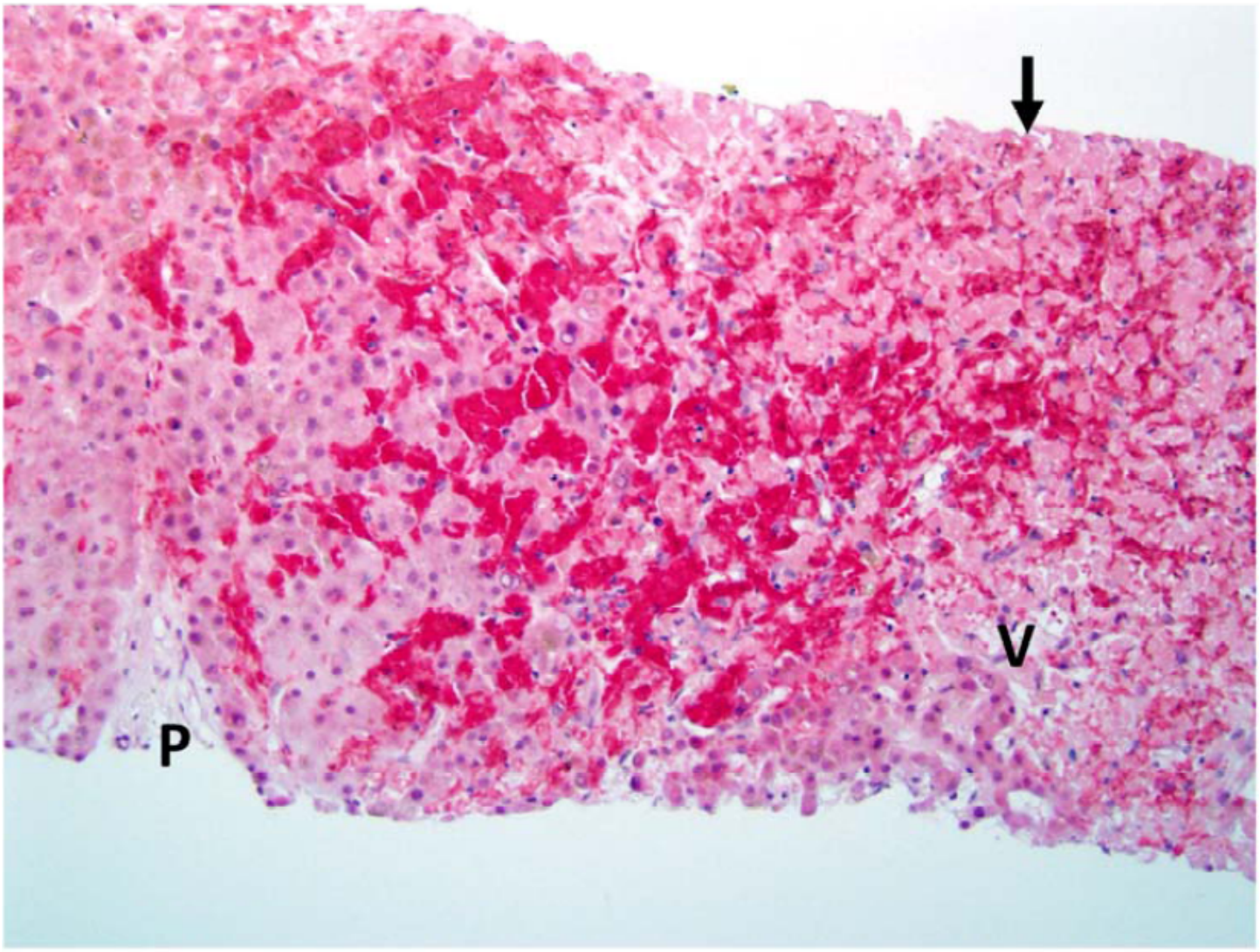
(See high resolution images)

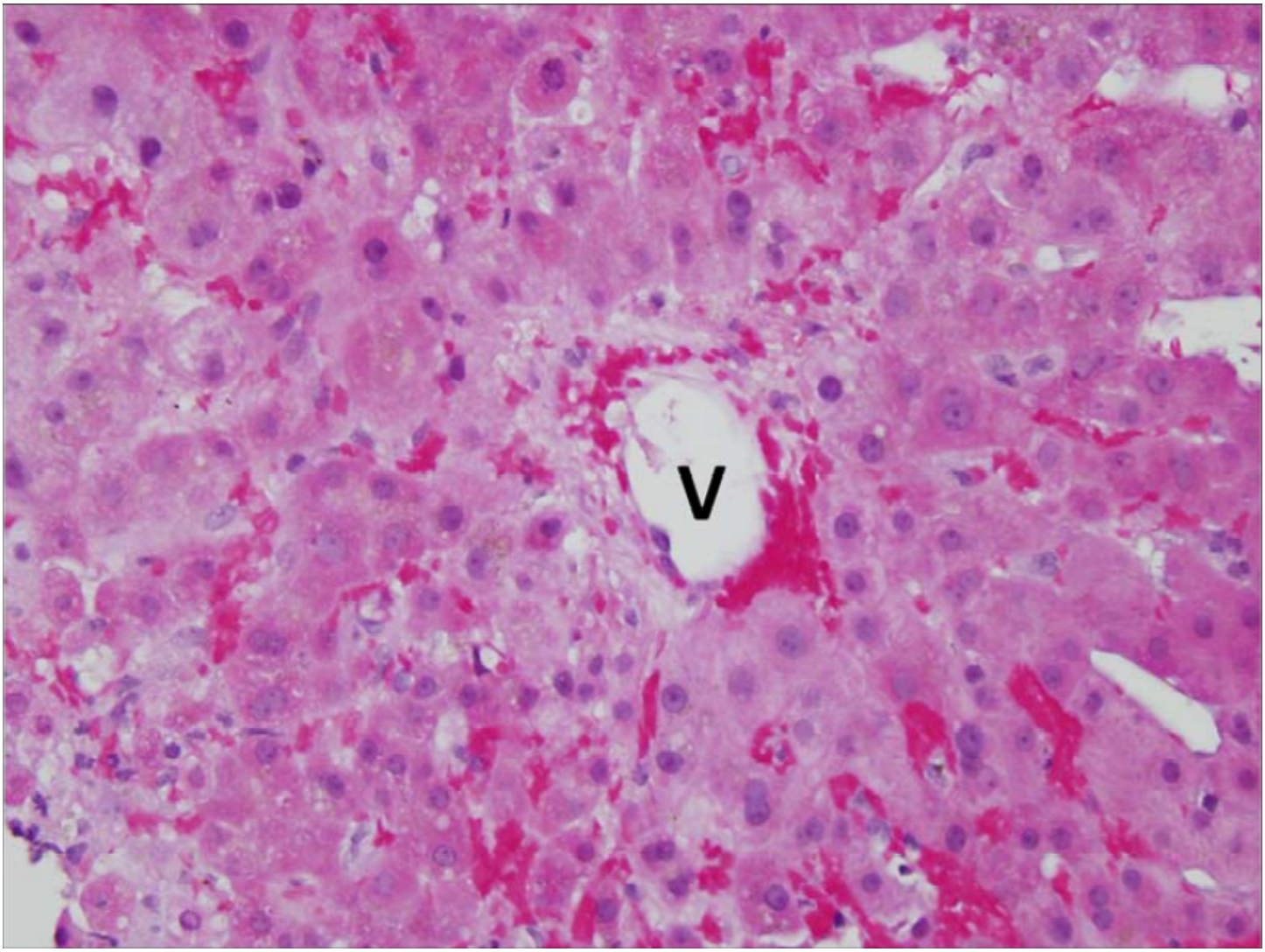



Sinusoidal Obstruction Syndrome

Histologic Features to Note:

This biopsy was taken from a 48 year old man who developed signs of sinusoidal obstruction syndrome following bone marrow transplantation. There is congestion and hemorrhage in zone 3 with spillage of red blood cells in between hepatocytes. This change is associated with hepatocyte necrosis (arrow). The central vein is not clearly seen, but the location is indicated (V). The portal area (P) is also marked for reference.

(See high resolution image)

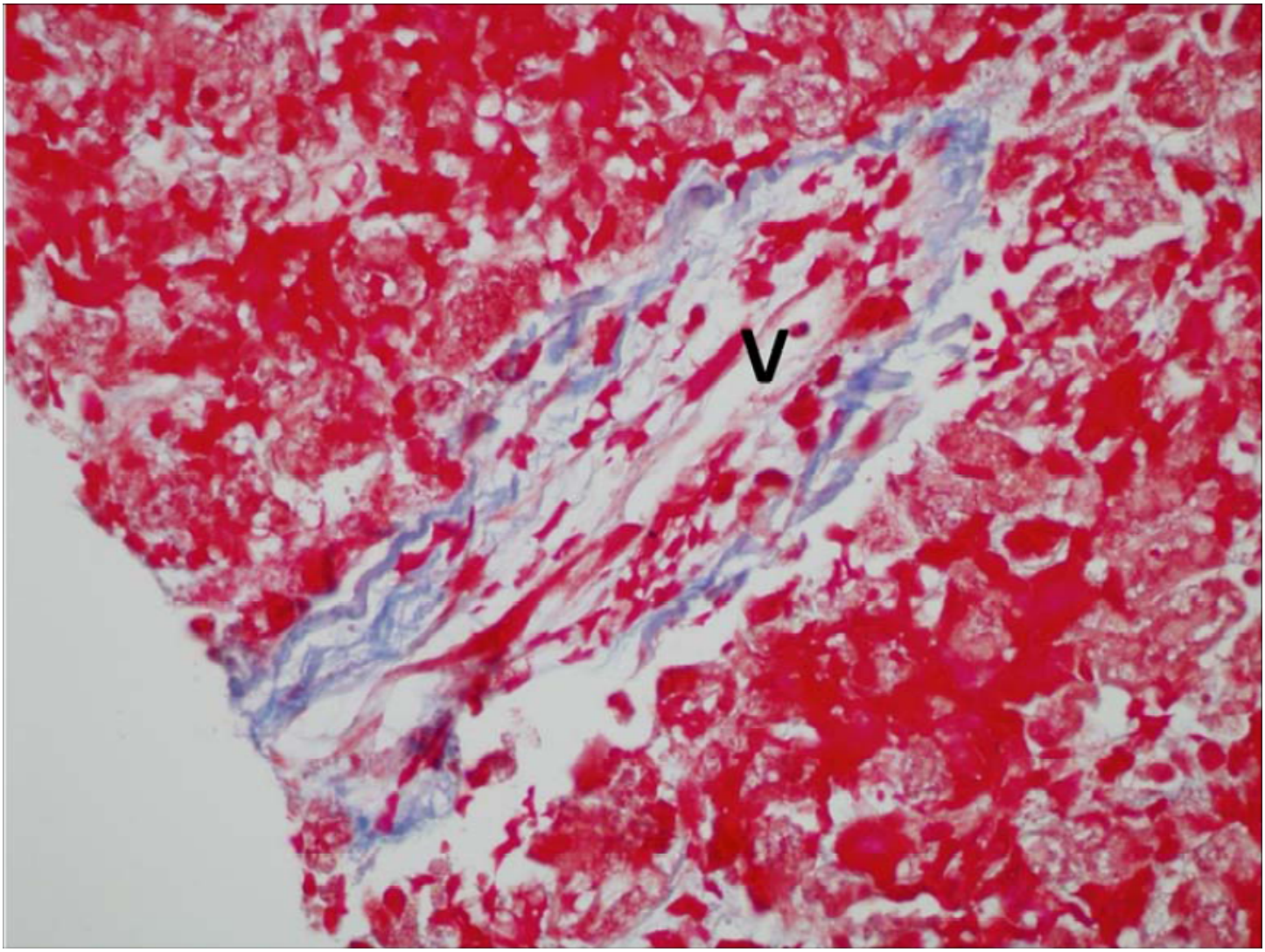



Sinusoidal Obstruction Syndrome

Histologic Features to Note:

Here a central vein (V) is clearly seen. There is hemorrhage in the vein wall and narrowing of the lumen by loose connective tissue.

(See high resolution image)




Sinusoidal Obstruction Syndrome

Histologic Features to Note:

On a Masson trichrome stain, the distinction between the original vein wall (stained blue) and the red colored strands of collagen within the vein lumen (V). In this section, the vessel lumen is almost completely occluded.

(See high resolution image)

## Selected References

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Willmot FC, Robertson GW. Senecio disease, or cirrhosis of the liver due to senecio poisoning. Lancet. 1920;2:848–9. Not in PubMed.

*(Outbreaks of a severe and often fatal disease presenting with abdominal pain and ascites among Europeans of poorer classes in South Africa were linked to eating wheat contaminated with seeds of Senecio plants which grow as weeds; a similar condition occurred in livestock and was reproduced in guinea pigs and rats).*

Bras G, Jeliffe DB, Stuart KL. Veno-occlusive disease of the liver with nonportal type of cirrhosis occurring in Jamaica. Arch Pathol. 1954;57:285–300. PubMed PMID: 13147641.

*(Description of 100 Jamaican-born patients, many infants and children, with liver disease marked by ascites, hepatomegaly and cirrhosis with histological findings of centrolobular congestion and collagen around occluded central veins, often with a history of drinking "bush tea").*

Reed GB, Cox AJ. The human liver after radiation injury: a form of veno-occlusive disease. Am J Pathol. 1966;48:597–611. PubMed PMID: 5327788.

*(Description of liver tissue from 12 patients with metastatic tumors who had received 3,000-5,900 rads of irradiation to the liver [5 also received alkylating agents]; early changes were centrolobular congestion, followed by central vein lesions and then occlusion and hepatic cell loss, consistent with a veno-occlusive process involving small branches of hepatic veins).*

Tandon BN, Tandon HD, Tandon RK, Narndranathan M, Joshi YK. An epidemic of veno-occlusive disease of liver in central India. Lancet. 1976;2:271–2. PubMed PMID: 59849.

*(Description of outbreak of 67 cases of veno-occlusive disease [ascites with only mild jaundice and no variceal hemorrhage] among 286 persons in 4 affected villages in central India, apparently due to contamination of wheat with seeds of Crotalaria species).*

Shulman HM, McDonald GB, Matthews D, Doney KC, Kopecky KJ, Gauvreau JM, Thomas ED. An analysis of hepatic venocclusive disease and centrilobular hepatic degeneration following bone marrow transplantation. Gastroenterology. 1980;79:1178–91. PubMed PMID: 7002704.

*(Analysis of liver biopsies from 204 patients who had undergone bone marrow transplantation for various malignancies, finding veno-occlusive disease in 27 patients, early lesions being centrilobular congestion, hepatocyte degeneration and subintimal edema within small central venules and later lesions fibrous obliteration of central venule lumina and fibrosis; correlated with more aggressive conditioning regimens).*

Erichsen C, Jönsson PE. Veno-occlusive liver disease after dacarbazine therapy (DTIC) for melanoma. J Surg Oncol. 1984;27:268–70. PubMed PMID: 6503301.

*(46 year old man with malignant melanoma developed abdominal pain and ascites after a third cycle of dacarbazine [bilirubin 3.1 mg/dL ALT 5282 U/L, Alk P 534 U/L, prothrombin index 12%] and died within days; autopsy showed veno-occlusive disease with eosinophilic infiltrates).*

McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. The clinical course of 53 patients with venocclusive disease of the liver after marrow transplantation. Transplantation. 1985;39:603–8. PubMed PMID: 3890288.

*(Among 255 patients undergoing bone marrow transplantation [now referred to as hematopoietic cell transplantation] for malignant disease, 53 [21%] developed veno-occlusive disease, marked by weight gain [93%] starting ~6 days after transplant followed by jaundice [98%: bilirubin 3.6-29.4 mg/dL], abdominal pain [75%], liver enlargement [68%]; 24 [45%] had serious progressive disease with ascites and hepatic encephalopathy and 17 [32%] died).*

Brugieres L, Hartmann O, Benhamou E, Zafrani ES, Caillaud JM, Patte C, Kalifa C, et al. Veno-occlusive disease of the liver following high-dose chemotherapy and autologous bone marrow transplantation in children with solid tumors: incidence, clinical course and outcome. Bone Marrow Transplant. 1988;3:53–8. PubMed PMID: 3048471.

*(Among 173 children undergoing 236 courses of high dose chemotherapy and hematopoietic cell transplantation, 39 children had hepatic abnormalities and 11 met the criteria for having veno-occlusive disease; syndrome marked by weight gain [decrease in sodium excretion] with weight gain of 5-12% followed by hepatomegaly and jaundice [bilirubin 4.5-26.9 mg/dL, ALT 60-1850 U/L, Alk P 1.5-2.5 times ULN]; 4 patients [2%] died).*

McDonald GB, Hinds MS, Fisher LD, Schoch HG, Wolford JL, Banaji M, Hardin BJ, 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;118:255–67. PubMed PMID: 8420443.

*(Prospective analysis of 355 patients undergoing hematopoietic cell transplantation; veno-occlusive disease developed in 54% and was severe in 16%, higher rates were associated with the combination of busulfan with cyclophosphamide [32%] and with total body irradiation [23%]; mortality rate being 98% in those with severe injury).*

Giles GJ, Kantarjian HM, Kornblau SM, Thomas DA, Garcia-Manero G, Waddelow TA, Dvid CL, et al. MyltotargTM (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. Cancer. 2001;92:406–13. PubMed PMID: 11466696.

*(Among 1119 patients with acute myeloid leukemia treated with gemtuzumab [calciheamicin-conjugated monoclonal anti-CD33], liver injury consistent with sinusoidal obstruction occurred in 14 [12%] 3 to 35 days after first dose, some of whom received no other cytotoxic agents; fatal outcome in 12 patients [10%]).*

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*(Review of clinical features, pathology, etiology, prevention and treatment of sinusoidal obstruction syndrome, a better term for this condition than veno-occlusive disease; first described in association with exposure to phytotoxins (pyrrolizidine alkaloids), the most common cause now is cancer chemotherapy and particularly myeloablative conditioning regimens in preparation for hematopoietic cell transplantation).*

Gooley TA, Rajvanshi P, Schoch HG, McDonald GB. Serum bilirubin levels and mortality after myeloablative allogeneic hematopoietic cell transplantation. Hepatology. 2005;41:345–52. PubMed PMID: 15660388.

*(Among 1419 patients undergoing bone marrow transplantation, nonrelapse mortality was 30% by day 200 and correlated with height of bilirubin and presence of multiorgan failure).*

McDonald GB. Review article: management of hepatic disease following haematopoietic cell transplant. Aliment Pharmacol Ther. 2006;24:441–52. PubMed PMID: 16886910.

*(Sinusoidal obstruction syndrome arises in first 20-30 days after hematopoietic cell transplant, case fatality rate is 15-20%, frequency ~38%, but frequency varies by risk factors [cyclophosphamide pharmacokinetics, preexisting liver disease, irradiation dose and use of gemtuzumab], no therapy has proven efficacious but defibrotide and repletion of glutathione deserve evaluation).*

McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology. 2010;51:1450–60. PubMed PMID: 20373370.

*(Review of liver complications of bone marrow [hematopoietic cell] transplantation, which have become less frequent with better understanding of their cause and means of prevention; the rate of sinusoidal obstruction syndrome has decreased because of avoidance of more aggressive ablative therapies [total body irradiation and high dose cyclophosphamide], better understanding of pharmacokinetics of the alkylating agents, and lower frequency of hepatitis C in marrow recipients).*

Richardson PG, Soiffer RJ, Antin JH, Uno H, Jin Z, Kurtzberg J, Martin PL, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant. 2010;16:1005–17. PubMed PMID: 20167278.

*(Trial of two doses of intravenous defibrotide in 149 patients with severe veno-occlusive disease after stem cell transplantation; 100 day survival was 42% with no differences between the two doses).*