3. Yee H, Lidofsky S. Fulminant hepatic failure. In: Feldman M, Sieisenger M, Scharschmidt E, eds. *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management.* Vol 2. Philadelphia, Pennsylvania; Saunders, 1998:1355-1364.
4. Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. *Gut*. 1998;42:576-580.
5. Rajvanshi P, Kowdley KV, Hirota WK, Meyers JB, Keeffe EB. Fulminant hepatic failure secondary to neoplastic infiltration of the liver. *J Clin Gastroenterol.* 2005;39:339-343.
6. Allison KH, Fligner CL, Parks WT. Radiographically occult, diffuse intrasinusoidal hepatic metastases from primary breast carcinomas: a clinicopathologic study of 3 autopsy cases. *Arch Pathol Lab Med.* 2004;128:1418-1423.
7. Morrison WL, Pennington CR. Liver metastases from an occult breast carcinoma presenting as acute fulminant hepatic failure. *Br J Clin Pract.* 1984;38: 273-274.
8. Myszor MF, Record CO. Primary and secondary malignant disease of the liver and fulminant hepatic failure. *J Clin Gastroenterol.* 1990;12:441-446.
9. Carty NJ, Foggit A, Hamilton CR, Royle GT, Taylor I. Patterns of clinical metastasis in breast cancer: an analysis of 100 patients. *Eur J Surg Oncol.* 1995; 21:607-608.
10. Roach H, Whipp E, Virjee J, Callaway MP. A pictorial review of the varied appearance of atypical liver metastasis from carcinoma of the breast. *Br J Radiol.* 2005;78:1098-1103.

Review

Metastatic Breast Cancer Presenting as Acute Liver Failure

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The clinical hallmarks of acute liver failure are coagulopathy (international normalized ratio ≥1.5) and hepatic encephalopathy in the absence of cirrhosis or preexisting liver disease that occur less than 26 weeks from symptom onset.[1] The vast majority of acute liver failure cases are related to drug toxicity; of these, acetaminophen is the leading cause of acute liver failure in the United States and Europe. Viral hepatitis, such as hepatitis B, as well as autoimmune liver disease and hypoperfusion or shock are also causes of many cases of acute liver failure.[1] Approximately 20–30% of acute liver failure cases have no identifiable etiology. The growing number of case reports and series describing malignant infiltration of the liver presenting as liver failure support raising the index of suspicion for neoplastic infiltration as a potential cause of cases with an unknown etiology.

Hepatic metastasis is not uncommon and has been identified in 40% of autopsies of adults with malignant tumors.[2] Most of these patients do not show signs or symptoms of liver disease. However, hepatic failure can occur as a result of metastatic disease infiltration to the liver, though this is very rare (accounting for only 0.44% in a large retrospective study).[3] These infrequent cases of liver failure have been described most commonly for hematologic malignancies, in particular non-Hodgkin lymphomas, but they can also be associated with solid tumors, including small-cell lung cancer and breast cancer.[2,4,5]

Breast cancer usually spreads to the bones, lungs, and/or liver.[6] Approximately 40–50% of women with metastatic breast cancer will have liver metastasis at some point during the course of their disease.[6] Hepatic metastasis can present at the time of diagnosis; however, particularly for patients diagnosed with invasive breast cancer, the metastatic process can occur several years later, even after treatment. Although most of these breast cancer metastases present as discrete masses or lesions that are easily seen in radiographic studies, they may occasionally manifest as diffuse infiltrating neoplasms that are not identified on radiologic studies.[6] Other times, this infiltrating tumor has a profound desmoplastic reaction that radiographically resembles cirrhosis. This entity is often called pseudocirrhosis or carcinomatous cirrhosis.[7]

The diffusely infiltrating type of metastasis has been most commonly associated with acute liver failure. Most reported cases of acute liver failure from metastatic breast cancer have occurred in patients with a prior history of known and adequately treated breast cancer. Ductal carcinomas of different degrees of invasiveness are by far the most frequently described. Women affected by this aggressive form of metastatic breast cancer are usually middle-aged, ranging from 35 to 63 years. The majority of patients present with 2–6 weeks of fatigue, nausea, anorexia, jaundice, worsening ascites, and different levels of altered mental status.[2,7-11] In addition, they have markedly elevated total bilirubin, aminotransferases, lactate dehydrogenase, and alkaline phosphatase levels, as well as thrombocytopenia, coagulopathy, and even disseminated intravascular coagulopathy. In a handful of cases, such as the one described by Goswami and associates,

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patients present with significant hepatic dysfunction but no hepatic encephalopathy.[12] Some patients present with portal hypertension, as manifested by esophageal variceal bleeding that requires endoscopic therapy.[7,8] Furthermore, in several cases in which a transjugular liver biopsy was performed to determine the etiology of the liver failure, an elevated hepatic-portal venous pressure gradient was found.[7,8,12]

In these cases of acute liver failure precipitated by metastatic breast cancer, the most common histologic finding is diffuse massive intrasinusoidal infiltration of the tumor. Some cases also have extensive fibrous tissue driven by a desmoplastic response.[7] Necrosis is also commonly seen and is associated with intravascular invasion and thrombus formation affecting tissue perfusion. It has been postulated that replacement of over 80–90% of hepatic parenchyma by the tumor could lead to jaundice and liver failure.[2] Other types of solid tumors, such as melanoma and gastric, prostate, and small-cell lung cancers, have presented as acute liver failure from tumor infiltration and with similar histologic findings to those described for metastatic breast cancer.[13-19]

Although the exact mechanisms that lead to this infiltrative pattern of metastatic spread are not clear, Allison and colleagues have proposed an interesting concept involving the adhesion proteins E-cadherin and CD44.[9] Both of these proteins play an important role in mediating cell-to-cell and cell-to-extracellular-matrix adhesion. The 3 cases of intrasinusoidal metastases that they described did not stain or express these proteins. It is thought that the loss of E-cadherin expression is necessary for metastasis to occur by facilitating cell detachment from the primary tumor. The absence of this molecule could explain single-cell infiltration. On the other hand, CD44 has been found to be overexpressed in different tumors, including breast cancer. Transendothelial migration of tumor cells is increased as a result of upregulated CD44 expression of breast cancer cell lines. This process is enhanced by hepatocyte growth factor. In the absence of CD44, carcinoma cells may not be able to invade across endothelial cells to create large metastatic lesions.[9] The lack of expression of these molecules could explain why malignant cells do not spread past sinusoids. Tissue hypoxia and injury, as well as oxidative stress, could then lead to a release of cytokines that promotes the development of liver failure in an already compromised hepatic parenchyma.[20]

Acute liver failure as a result of an infiltrating hepatic malignancy is associated with a rapid and aggressive course of clinical deterioration and a very poor prognosis. These patients are treated with supportive care and intensive medical management, as active malignancy is an absolute contraindication for liver transplantation. The use of chemotherapeutic agents is also frequently limited by markedly elevated bilirubin levels and impaired hepatic function, as well as concomitant infections and multi-organ failure.[6] Nonetheless, early recognition and diagnosis of the etiology of acute liver failure could impact at least short-term survival in this patient population. Achieving this goal requires prompt biochemical, serologic, and histologic investigation along with medical management in an intensive care unit, preferably by a multidisciplinary team of physicians that includes hepatologists, intensivists, and oncologists.

References

1. Polson J, Lee WM; American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology.* 2005;41:1179-1197.
2. Bégin LR, Boucher D, Lamoureux E. Diffuse hepatic intravascular carcinomatous embolization resulting in fatal liver failure: a clinicopathologic study of 4 cases. *Pathol Res Pract.* 2001;197:433-440.
3. Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. *Gut*. 1998;42:576-580.
4. Morali GA, Rozenmann E, Ashkenazi J, Munter G, Braverman DZ. Acute liver failure as the sole manifestation of relapsing non-Hodgkin's lymphoma. *Eur J Gastroenterol Hepatol.* 2001;13:1241-1243.
5. Lettieri CJ, Berg BW. Clinical features of non-Hodgkins lymphoma presenting with acute liver failure: a report of five cases and review of published experience. *Am J Gastroenterol.* 2003;98:1641-1646.
6. Diamond JR, Finlayson CA, Borges VF. Hepatic complications of breast cancer. *Lancet Oncol.* 2009;10:615-621.
7. Sass DA, Clark K, Grzybicki D, Rabinovitz M, Shaw-Stiffel TA. Diffuse desmoplastic metastatic breast cancer simulating cirrhosis with severe portal hypertension: a case of "pseudocirrhosis". *Dig Dis Sci.* 2007;52:749-752.
8. Agarwal K, Jones DE, Burt AD, Hudson M, James OF. Metastatic breast carcinoma presenting as acute liver failure and portal hypertension. *Am J Gastroenterol.* 2002;97:750-751.
9. Allison KH, Fligner CL, Parks WT. Radiographically occult, diffuse intrasinusoidal hepatic metastases from primary breast carcinomas: a clinicopathologic study of 3 autopsy cases. *Arch Pathol Lab Med.* 2004;128:1418-1423.
10. Myszor MF, Record CO. Primary and secondary malignant disease of the liver and fulminant hepatic failure. *J Clin Gastroenterol.* 1990;12:441-446.
11. Lowenthal A, Tur-Kaspa R, Brower RG, Almog Y. Acute liver failure complicating ductal breast carcinoma: two cases and literature review. *Scand J Gastroenterol.* 2003;38:1095-1096.
12. Goswami R, Babich M, Farah KF. Occult breast malignancy masquerading as acute hepatic failure. *Gastroenterol Hepatol (N Y).* 2011;7:62-65.
13. Montero JL, Muntané J, de las Heras S, Ortega R, Fraga E, De la Mata M. Acute liver failure caused by diffuse hepatic melanoma infiltration. *J Hepatol.* 2002;37:540-541.
14. Te HS, Schiano TD, Kahaleh M, et al. Fulminant hepatic failure secondary to malignant melanoma: case report and review of the literature. *Am J Gastroenterol.* 1999;94:262-266.
15. Shakir FA, Madhoun M, Whorton J, Harty R. Metastatic prostatic carcinoma presenting as fulminant hepatic failure. *South Med J.* 2008;101:1049-1050.
16. Athanasakis E, Mouloudi E, Prinianakis G, Kostaki M, Tzardi M, Georgopoulos D. Metastatic liver disease and fulminant hepatic failure: presentation of a case and review of the literature. *Eur J Gastroenterol Hepatol.* 2003;15:1235-1240.
17. Sawabe M, Kato Y, Ohashi I, Kitagawa T. Diffuse intrasinusoidal metastasis of gastric carcinoma to the liver leading to fulminant hepatic failure. A case report. *Cancer.* 1990;65:169-173.
18. Rajvanshi P, Kowdley KV, Hirota WK, Meyers JB, Keeffe EB. Fulminant hepatic failure secondary to neoplastic infiltration of the liver. *J Clin Gastroenterol.* 2005;39:339-343.
19. Gilbert J, Rutledge H, Koch A. Diffuse malignant infiltration of the liver manifesting as a case of acute liver failure. *Nat Clin Pract Gastroenterol Hepatol.* 2008;5:405-408.
20. Smedsrod B, Le Couteur D, Ikejima K, et al. Hepatic sinusoidal cells in health and disease: update from the 14th International Symposium. *Liver Int.* 2009;29:490-501.