Session 2. Mimickers of Hepatic Malignancy: What to Do?

New lesions found during treatment of extrahepatic malignancy

Won Jin Chang

Division of Hematology-Oncology, Department of Medicine,
Korea University Medical Center, Korea

Curriculum Vitae

2006-2007	Internship, Korea University Medical Center, Seoul, Korea
2008-2012	Residentship, Department of Medicine, Korea University Medical Center, Seoul, Korea
2012-2013	Fellowship, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Seoul, Korea
2014-present	Fellowship, Division of Hematology-Oncology, Department of Medicine, Korea University Medical Center, Seoul, Korea

New lesions found during treatment of extrahepatic malignancy

Introduction

As clinicians, we need to be aware of the radiologic manifestations of chemotherapy on the liver, since this is a major organ responsible for drug clearance and synthetic function of many bio-chemical pathways. Todays' topic will focus primarily on different chemotherapeutic agents and how different sub-classes can affect the liver, and then also focus on the more common imaging findings of the liver in patients undergoing treatment with chemotherapy.

Classes of chemotherapeutic agents

Cytotoxic chemotherapy agents exhibit their affects by interfering with DNA and RNA synthesis as well as cell division. These include alkylating agents, anti-metabolites, anti-tumor antibiotics, isomerase inhibitors, mitotic inhibitors. Also, advances in understanding cancer cell biology have led to the development of molecular therapies, which target specific signaling pathways. Many of these agents affect multiple targets, and therefore have the potential to inhibit molecules that are critical to unsuspected pathways, causing toxicity that can sometimes be unpredictable.

Table 1. Classes of chemotherapeutic agents

Class	Mechanism	Examples
Alkylating agents	DNA damage, not phase specific	Platinums (cisplatin, carboplatin, oxaliplatin), nitrogen mustard derivatives (cytoxan, chlorambucil), alkyl sulfonates, nitrosourea (carmustine, lomustine), triazines
Anti-metabolites	DNA/RNA replication in S phase of cell division	Pyrimidine analogues (gemcitabine, 5-fluorouracil, capecitabine), methotrexate, gemcitabine-gemzar, 6 mercaptopurine, cytarabine
Anti-tumor antibiotics	Interfere with enzymes needed for DNA replication	Doxorubicin-adriamycin, danorubicin, mytomycin C, bleomycin
Isomerase inhibitors	Interfere with enzymes needed for DNA replication	Topotecan, irinotecan
Mitotic inhibitors	Plant alkaloids that inhibit mitosis in tumor cells	Taxanes-TAXOL, taxotere, vinca alkaloids (vincristine, vinblastine), etramustine - emcyt
Hormone therapy	Alter the action and production of hormones	Anti-estrogens (tamoxifen), aromatase inhibitors (arimedex), progestins (megesterol acetate), estrogens
Immuno-therapy	Stimulates immune system to recognize and attack cancer cells	Monoclonal antibody(rituximab), immunotherapy: BCG, interleukin2, alpha interferon immunomodulating: thalidomide, enalidomide
Differentiating agents	Act on cancer cells to make them differentiate to normal cells	Retinoids, tretinoin(ATRA, atralin) bexarotene targretin, arsenic trioxide(arsenox)
Targeted therapies	More specific than traditional chemotherapies; attack cells with mutant version of certain genes	Imatinib-Gleevec, gefitinib Iressam erlotinib Tarceva, sunitinib Sutent and bortezomib
Steroids	Decreases inflammation and enhance effect of other drugs	Prednisone Methylprednisolone Dexamethasone (decadron)

Hepatotoxicity of chemotherapeutic agents and imaging findings

Sinusoidal obstructive syndrome

Hepatic SOS, previously called veno-occlusive disease is a pattern of vascular liver injury caused by microvascular deposition of fibrous material impairing the normal flow of small intrahepatic veins. SOS can result from high-dose chemotherapy given prior to bone marrow transplant and intensive chemotherapy, usually with cyclophosphamide, is most closely associated with the development of a rapidly progressive, occlusive disease of small hepatic venules due to en-dothelial-cell injury. SOS has been reported with notable chemotherapy agents such as oxaliplatin, 6-MP, dacarbazine, cyclophosphamide, and vincristine.

Computed tomography (CT) and ultrasonographic findings of hepatic SOS includes hepatosplenomegaly, ascites, gallbladder wall thickening, periesophageal varices and recanalization of umbilical veins. On post-contrast CT and MRI, patchy liver enhancement and narrowing of main hepatic veins were reported as frequent.

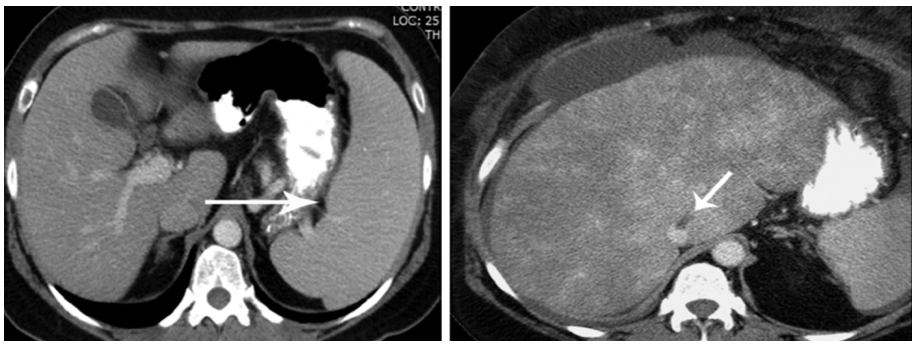

Fig. 1. Hepatic sinusoidal obstructive syndrome: (L) sinusoidal congestion with features of portal hypertension, splenomegaly and (R) mottled enhancement of the liver representing congestion thrombocytopenia.

Pseudocirrhosis

"Pseudocirrhosis" is a radiologic term used to describe the serial development of diffuse hepatic nodularity caused by chemotherapy for metastatic disease of the liver. This can especially be seen in both metastatic breast and colon cancer. Pseudocirrhosis is defined by morphology changes in the liver parenchyma that mimics liver cirrhosis, and can cause retracted tumor tissue and scarring. Pseudocirrhosis, while a potential cause of portal hypertension and liver failure, does not show the true clinical features of cirrhosis and loss of synthetic function.

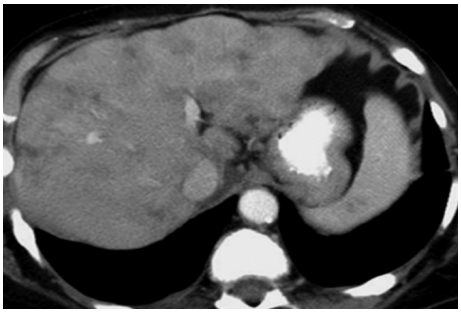

Fig. 2. Pseudocirrhosis: macronodular liver with fibrosis following completion of therapy.

Fatty liver

Chemotherapy (eg 5-FU, platinum derivatives & taxanes) causes oxidative stress in cancer cells and normal cells leading to hepaticsteatosis. Distribution of fatty liver disease can vary from diffuse infiltration to focal steatosis.

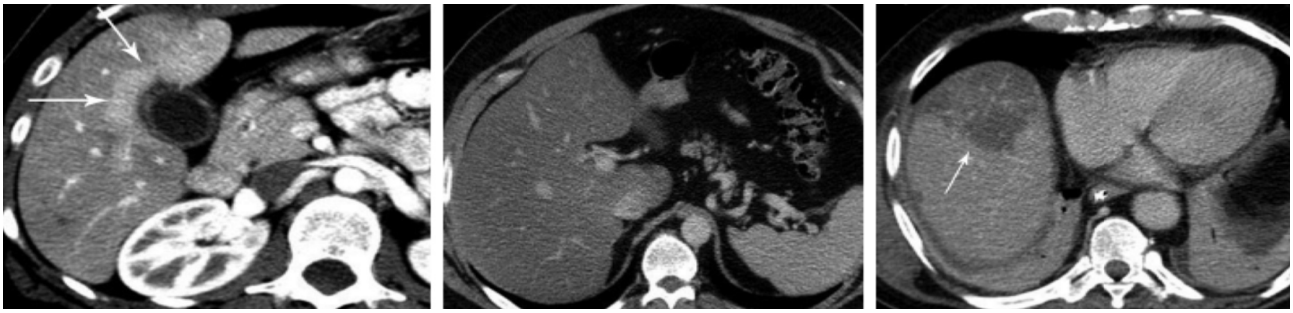

Fig. 3. Steatosis patterns

Hepatic necrosis

A more severe and dreaded consequence of liver injury from chemotherapy is the development of acute liver failure from hepatic necrosis. Essentially, chemotherapy drugs that can induce an acute hepatitis can likely cause hepatic necrosis.

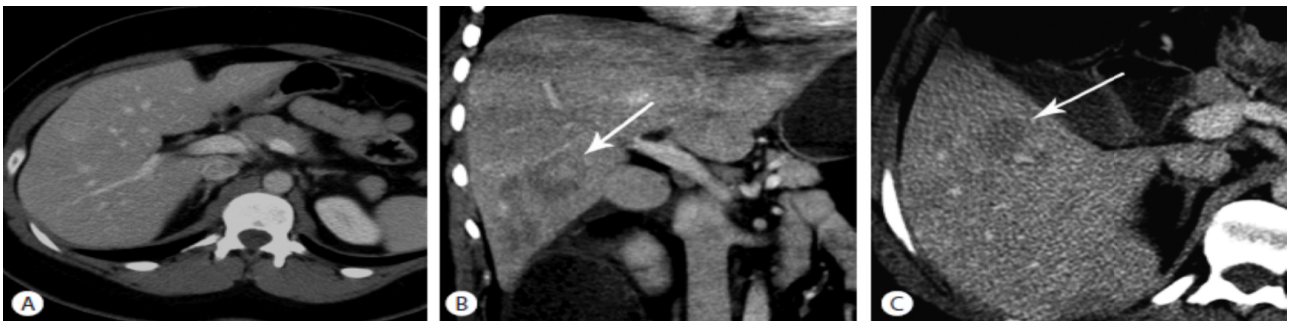

Fig. 4. Hepatic Necrosis. (A) The pretreatment image shows no abnormality in liver (B) (C) After chemotherapy, coronal (B) and axial (C) contrast enhanced CT images demonstrate focal liver necrosis vs peliosis-centrilobular hemorrhagic necrosis of the liver (arrows).

Portal vein thrombosis

Portal vein thrombosis (PVT) has rarely been described during antineoplastic chemotherapy. However, in adults, a few cases have been reported following chemotherapy treatment of L-asparaginase, Autologous stem cell transplantation, and after haematopoetic cell transplantation.

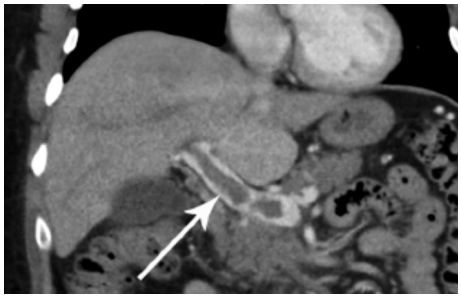

Fig. 5. Filling defect in the portal vein (white arrow) compatible with portal vein thrombosis

Conclusion

Cancer chemotherapy may be toxic to the liver, and recognition of patterns of liver injury is crucial to the clinician and radiologist. Conditions such as SOS, steatosis, pseudocirrhosis, and even hepatic necrosis can occur as a direct result of chemotherapy, which may simulate a clinical presentation of long term hepatic damage and cirrhosis. Imaging recognition of these conditions can allow the radiologists and clinicians to effect the appropriate management to reduce morbidity and mortality

References

1. Torrisi JM, Schwartz LH, Gollub MJ, Ginsberg MS, Bosl GJ, Hricak H. CT findings of chemotherapy-induced toxicity: what radiologists need to know about the clinical and radiologic manifestations of chemotherapy toxicity. Radiology 2011;258:41-56.
2. King PD, Perry MC. Hepatotoxicity of chemotherapy. Oncologist 2001;6:162-176.
3. Seo AN, Kim H. Sinusoidal obstruction syndrome after oxaliplatin-based chemotherapy. Clin Mol Hepatol 2014;20:81-84.
4. Overman MJ, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, et al. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol 2010;28:2549-2555.
5. Jeong WK, Choi SY, Kim J. Pseudocirrhosis as a complication after chemotherapy for hepatic metastasis from breast cancer. Clin Mol Hepatol 2013;19:190-194.
6. Kang SP, Taddei T, McLennan B, Lacy J. Pseudocirrhosis in a pancreatic cancer patient with liver

metastases: a case report of complete resolution of pseudocirrhosis with an early recognition and management. World J Gastroenterol 2008;14:1622-1624.

7. Fernandez FG, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg 2005;200:845-853.
8. Ankush Sharma, Roozbeh Houshyar. Chemotherapy induced liver abnormality: imaging perspective. Clinical and Molecular Hepatology 2014;20:317-324