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CASE REPORT

Docetaxel Induced Sclerosing Cholangitis

Jennifer L. Horsley-Silva[1] · Elizabeth N. Dow[2] · Christine O. Menias[3] · Maxwell L. Smith[4] · Estrella M. Carballido[2] · Keith D. Lindor[1] · Hugo E. Vargas[1]

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Abbreviations

CT	Computer tomography
MRI	Magnetic resonance imaging
LITs	Liver injury tests
ADT	Androgen deprivation therapy

A 78-year-old gentleman was referred for hepatology consultation. One year prior, he was diagnosed with metastatic high-grade prostate adenocarcinoma. Dual androgen deprivation therapy (ADT) with leuprolide and bicalutamide was started, and he underwent 43 fractions of palliative radiation to the pelvis. Due to evidence of improved survival outcomes with combination ADT and docetaxel in hormonal-sensitive metastatic prostate cancer, chemotherapy was initiated [1]. Prior to initiation of docetaxel, his liver injury tests (LITs) were normal, and computer tomography (CT) of the abdomen and pelvis demonstrated normal liver appearance. Docetaxel was initiated using every 3 week dosing (75 mg/m^2, total dose = 134 mg), and after administration, the patient developed elevated LITs for the first time: alkaline phosphatase 197 u/l, alanine aminotransferase (ALT) 67 u/l, aspartate aminotransferase (AST) 59 u/l, and total bilirubin 0.9 mg/dl. Patient was asymptomatic, no evidence of abdominal pain, jaundice, or pruritus. He was switched to weekly docetaxel due to side effects (30 mg/m^2 weekly, total dose = 54 mg); however, LITs elevation continued: alkaline phosphatase 518 u/l, ALT 144 u/l, AST of 90 u/l, and total bilirubin of 0.8 mg/dl. Repeat CT demonstrated new diffuse intrahepatic biliary dilatation with periductal enhancement suggestive of a diffuse cholangitis picture (Fig. 1). Docetaxel was held, and patient was monitored. After 2 months without resolution of abnormal LITs, magnetic resonance imaging (MRI) was pursued, demonstrating continued multifocal narrowing and dilatation of intrahepatic bile ducts, including peripheral bile ducts, with the appearance of sclerosing cholangitis (Fig. 2). An IgG4 level was normal. Liver biopsy 2 months later was performed to determine whether further chemotherapy should be continued, and because of limited evidence that metastatic prostate cancer can simulate sclerosing cholangitis [2]. Biopsy revealed features of subacute bile duct obstruction and stricturing with moderate hepatocanalicular cholestasis, and reactive changes as evidenced by numerous eosinophils. There was biliary-type bridging fibrosis with no architectural distortion or regenerative nodules (Fig. 3). These findings are consistent with a drug-induced inflammation and sclerosing cholangitis. Five months later, imaging portrayed continued evidence of secondary sclerosing cholangitis.

Docetaxel (Taxotere®) is a potent semisynthetic derivative of paclitaxel, a member of the taxane class of chemotherapy that works by binding to microtubules and

✉ Hugo E. Vargas
vargas.hugo@mayo.edu

[1] Division of Gastroenterology and Hepatology, Department of Transplant Hepatology, Mayo Clinic, 5777 East Mayo Boulevard, Phoenix, AZ 85054, USA

[2] Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, AZ, USA

[3] Division of Radiology, Mayo Clinic, Phoenix, AZ, USA

[4] Division of Laboratory Medicine and Pathology, Mayo Clinic, Phoenix, AZ, USA

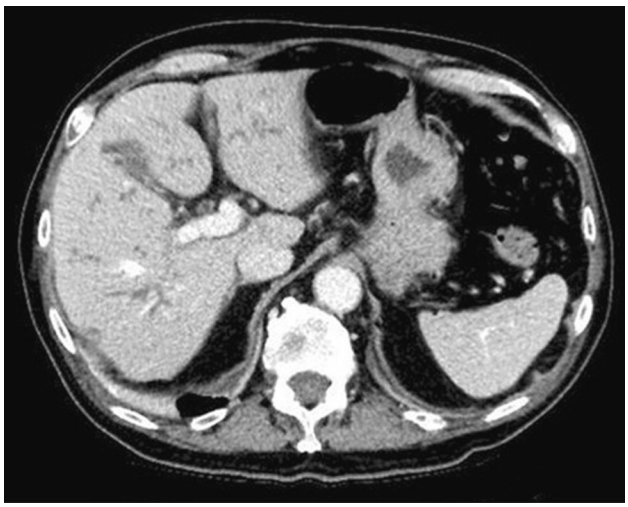

Fig. 1 CT demonstrating new diffuse intrahepatic biliary dilatation with periductal enhancement suggestive of a diffuse cholangitis picture

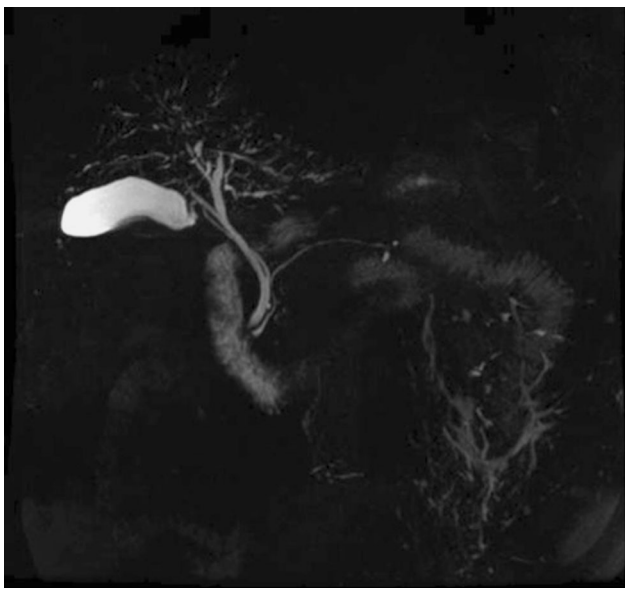

Fig. 2 MRI demonstrating continued multifocal narrowing and dilatation of intrahepatic bile ducts, including peripheral bile ducts, with the appearance of sclerosing cholangitis

inhibiting mitosis. It is known that docetaxel has large interindividual variability in pharmacokinetics and this variability is related to both toxicity and efficacy [3, 4]. Docetaxel undergoes extensive hepatic metabolism, biliary excretion, and fecal elimination. It is transported from the blood into hepatocytes by organic anion transporting peptides 1B1 and 1B3 and metabolized by cytochrome P450 3A isoforms CYP3A5 and to a lesser extent, CYP3A5 [4]. Docetaxel and its metabolites are excreted into the bile via ABCB1- and ABCC2-mediated transport [5]. Known side

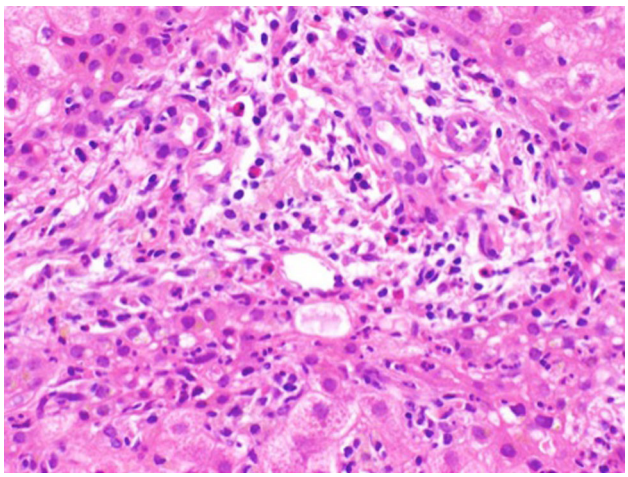

Fig. 3 Pathology specimen, stained with H&E, demonstrating subacute bile duct obstruction and stricturing with moderate hepatocanalicular cholestasis, and reactive changes as evidenced by numerous eosinophils, consistent with drug-induced inflammation and sclerosing cholangitis

effects can include hepatotoxicity in the form of elevated LITs, which was the initial presentation of this patient [6]. However, to our knowledge, it has never been associated with inducing secondary sclerosing cholangitis.

The patient had three drug–drug interactions that could have led to increased docetaxel concentrations: carvedilol inhibits the transporter ABCB1, decreasing elimination; bicalutamide inhibits CYP3A4 the primary route of metabolism; and dronedarone inhibits CYP3A4 and ABCB1 [7–9]. When all three interactions are taken into account, in addition to large interindividual variability in pharmacokinetics, the level of docetaxel could potentially be much higher in this patient compared to others.

The patient demonstrated no signs of primary sclerosing cholangitis, and given the correlation of timing and direct comparison imaging showing the distinct changes of bile ducts associated with drug administration and LIT changes, without other cause being identified, it appears this patients secondary sclerosing cholangitis is caused by docetaxel [10]. We hypothesize that the increase in docetaxel concentrations could have led to drug-induced inflammation and biliary stasis.

Compliance with ethical standards

Conflict of interest None.

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