A case report of veno-occlusive disease (VOD) in a patient with metastatic triple-negative breast cancer receiving trastuzumab deruxtecan

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Background

Antibody drug conjugates (ADCs)

- Approved for a variety of both solid tumor and malignant hematologic conditions, including HER2-low breast cancer.[1]
- Fam-trastuzumab deruxtecan-nxki (T-DXd) is an ADC that combines the anti-HER2 monoclonal antibody, trastuzumab, to a highly potent topoisomerase I inhibitor payload.[2]
- Common side effects of T-DXd are bone marrow suppression and GI effects; more serious adverse effects include pneumonitis and left ventricular dysfunction.[3]

Veno-occlusive disease (VOD; also known as sinusoidal occlusive disease)

- Results from damage to the small blood vessels in the liver, leading to obstruction of blood flow, volume overload, and potentially liver failure; it can rapidly progress to multiorgan failure.[4-6]
- Symptoms include tender hepatomegaly, rapid weight gain, ascites, as well as rapid elevations in bilirubin and transaminases.[4-6]
- VOD is a known and rare side effect of some ADCs, however it has not been reported with the use of T-DXd. **We present a rare case of VOD secondary to trastuzumab deruxtecan in a patient with metastatic breast cancer.**

Case Report

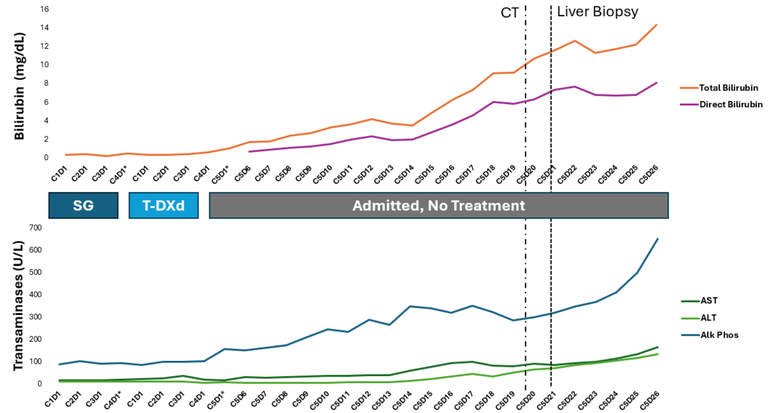
45-year-old female with stage IIIA triple negative breast cancer [ER 0%, PR 0%, HER2 IHC 2+, FISH Neg]

- Neoadjuvant Pembrolizumab Taxol/Carboplatin -> Adriamycin/ Cyclophosphamide
  - Neoadjuvant pembrolizumab stopped after 3 doses due to steroid-refractory colitis, which resolved with vedolizumab.
- Underwent mastectomy, SLNBx and found to have residual disease (ypT1b, ypN0; RCB1)
- Developed metastatic recurrence while on adjuvant capecitabine

In the metastatic setting, the tumor rapidly progressed through 1L sacituzumab govitecan (SG) and she was started on 2L T-DXd.

Clinical Data

Figure 1: After cycle 4 of T-DXd, she developed rapid elevations of total and direct bilirubin and mild elevation in transaminases.



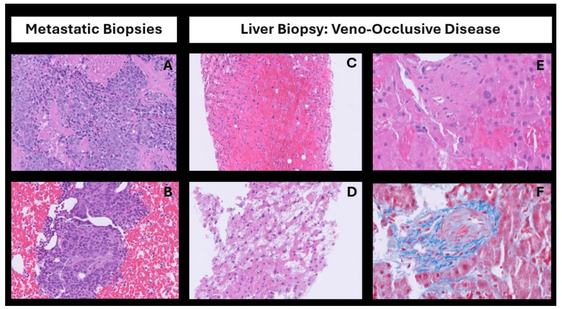
*ALT = alanine aminotransferase; Alk Phos = alkaline phosphatase; AST = aspartate aminotransferase; C = cycle, D = Day; *ADC dose not given*

Figure 2: No evidence of hepatic metastases (C5D20)



CT Chest with similar abutment of the right hepatic lobe by the right chest wall mass (red arrow) with compression on the parenchyma, possibly with invasion. <u>No intrahepatic lesion is seen.</u>

Figure 3: A liver biopsy (C5D21) confirmed venous outflow obstruction consistent with VOD. No metastatic cancer found.



<u>Metastatic Biopsies.</u>

A: Pleural biopsy demonstrating metastatic breast carcinoma

B: Bone marrow clot section showing metastatic carcinoma (Hematoxylin-eosin, A and B, x200)

<u>Liver Biopsy: Veno-Occlusive Disease</u>

C and D: Demonstrates zone 3 sinusoidal dilation and congestion (Hematoxylin-eosin, A, x100 and B, x200

E and F: The central hepatic vein shows fibrous obliteration by collagen (Hematoxylin-eosin, A and B, X400)

<u>Case Treatment</u>: Defibrotide was considered for VOD treatment but given extent of metastatic breast cancer, progressive hepatic dysfunction and a declining functional status, the patient was transitioned to hospice. A Medwatch report was filed with the FDA.

Discussion

- **VOD is likely underdiagnosed in patients with solid tumors** like breast cancer, as most patients have unresectable or metastatic disease in the liver where many of the signs and symptoms of progression may overlap with VOD.
- Our patient had several risk factors for the development of VOD, including prior receipt of chemotherapy in addition to T-DXd.[7]
  - **<u>Risk factors include</u>**: prior chemotherapy, older age, poor performance status, and underlying liver dysfunction or metabolic syndrome
- Management of VOD includes supportive care in mild cases and defibrotide in severe cases. **Prognosis depends on severity but is generally poor**.[8,9]
- While VOD is rare in patients with solid malignancies, outcomes from ADC-induced VOD is likely poor because **ADCs are often utilized in the advanced or metastatic setting, where hepatic dysfunction may exclude or pause systemic therapies allowing progression of metastatic disease**.
- Given the increasing use of ADCs in breast cancer and many other malignancies, as well as the ongoing development of new ADCs, **it is critical to consider VOD as a cause of rising liver enzymes in patients without clear evidence of disease progression**.

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References: available upon request