

Chemotherapy-associated steatohepatitis (CASH) Mimicking Cancer Progression: A Case Report with Suspected Topotecan Association

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INTRODUCTION

- Chemotherapy-associated steatohepatitis (CASH) is an underrecognized form of drug-induced liver injury.
- Radiographically, it can mimic hepatic metastases, particularly on CT imaging
- CASH is associated with:
 - Irinotecan
 - 5-fluorouracil
 - Methotrexate
 - Tamoxifen
- Misdiagnosis may lead to:
 - Inappropriate administration of chemotherapy
 - Increased cumulative toxicity
 - Psychological harm to the patient via biopsychosocial model

OBJECTIVE

- Highlight CASH as a diagnostic pitfall in oncology
- Demonstrate the limitations of imaging alone as a metric of malignancy response or progression
- Emphasize the importance of repeat biopsy when radiographic discordance exists
- Present a potential novel association of CASH with topotecan

CASE PRESENTATION

- 64 year-old female with limited-stage combined lung adenocarcinoma and large cell neuroendocrine carcinoma with hepatic metastases
- PMH: psoriatic arthritis, type 1 diabetes mellitus, hypertension, peripheral neuropathy, former tobacco use (15 pack-year history, quit at the age of 58), and otosclerosis requiring stapes prosthesis implantation (approximately 20 years ago)
- Found to have a 1.3 x 1.0 cm RUL nodule with FDG avidity on PET-CT.
- Biopsy + for lung adenocarcinoma with neuroendocrine cells
- Of note, patient could not undergo MRI due to stapes prosthesis (unable to obtain serial #)

CHEMOTHERAPY TIMELINE

- 11/2021 - completed Carboplatin/Etoposide x4 cycles
- Post-treatment imaging demonstrated multiple small hepatic lesions suspicious for metastatic disease
- 3/2022 - Liver biopsy: benign fatty changes
- 5/2022 – Carboplatin / Paclitaxel / Pembrolizumab x4 cycles given high suspicion for metastatic disease
- 8/2022 – numerous liver lesions on imaging – Lurbinectedin

- 1/2023 – Topotecan
- 3/2023 – CT A/P - hepatic metastases appear more numerous since prior
- 3/2023 – Docetaxel / Ramucirumab
- 3/2024 – low-dose Paclitaxel / Gemcitabine
- 5/2024 – CT A/P progression of small hepatic lesions
- 5/2024 – Gemcitabine
- 7/2024 – CT A/P: innumerable low-attenuation lesions throughout liver have increased, consistent with metastases
- 7/2024 – Carboplatin / Etoposide x4 cycles
- 9/2024 – CT A/P: significant interval improvement in innumerable low-attenuation liver lesions consistent with treatment response
- 1/2025 – care assumed under new team
- 2/2025 – underwent biopsy of liver area of suspicion: benign liver parenchyma with severe steatosis
- Surveillance - No further chemotherapy

IMAGING

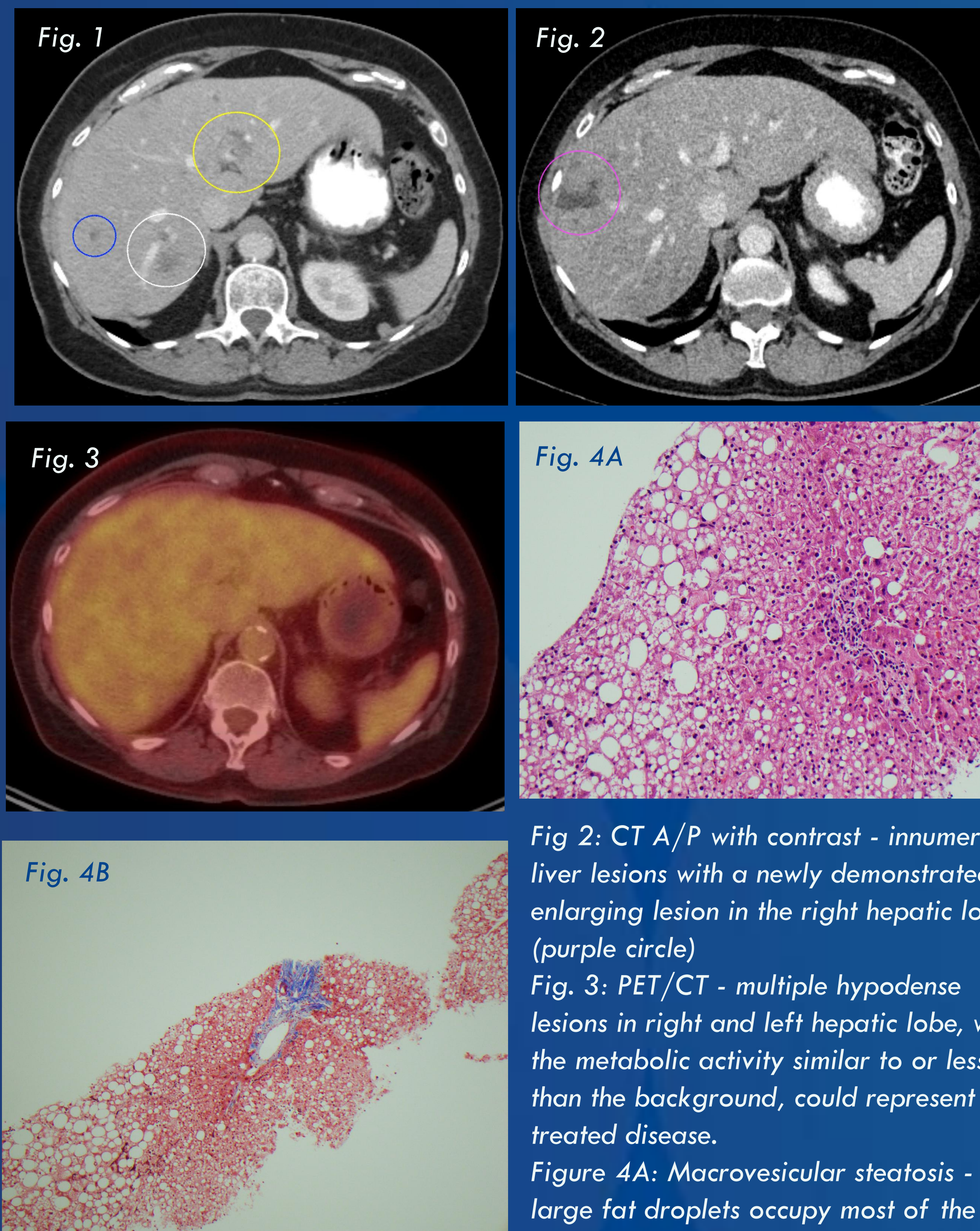


Fig. 1: CT A/P with contrast - There are multiple hypoattenuating lesions throughout the liver consistent with metastases, for example, a 1.8 x 2.0 cm lesion in segment VII (white circle). A 0.8cm lesion (blue circle)

Fig. 2: CT A/P with contrast - innumerable liver lesions with a newly demonstrated, enlarging lesion in the right hepatic lobe (purple circle)
 Fig. 3: PET/CT - multiple hypodense lesions in right and left hepatic lobe, with the metabolic activity similar to or less than the background, could represent treated disease.
 Figure 4A: Macrovesicular steatosis - large fat droplets occupy most of the hepatocyte cytoplasm
 Figure 4B: Perivenular and periportal fibrosis

DISCUSSION

- 1) Mechanism of CASH appears to vary depending on the culprit, but common to all is impairment of mitochondrial function and oxidative stress to hepatocytes¹
- 2) Risk factors for CASH: obesity, diabetes mellitus, and hyperlipidemia². Successive chemotherapy regimens in an individual patient, may dispose one to an increased risk of developing CASH (2). In addition, risk may be cumulative when anti-neoplastics are combined together in one treatment regimen, such as in colorectal cancer where the combination FOLFIRINOX (5-FU, Irinotecan, and Oxaliplatin) is often given³
- 3) Diagnostic pitfall – imaging studies alone are not always sufficient to portray clinical progression
 - In this case, “hypodense liver lesions consistent with metastatic liver disease” was likely steatohepatitis without malignancy all along
 - CT cannot reliably distinguish metastases vs focal steatosis
 - PET/CT with low metabolic activity argues against malignancy
- 4) Obtain repeat biopsy when diagnostic uncertainty exists
 - Repeat biopsy should be obtained at time of recurrence to identify resistance and redirect treatment⁴
- 5) Topotecan possible first-described association with CASH
 - Irinotecan has been previously described in literature
 - Biologic plausibility via **topoisomerase I inhibition interfering with mitochondrial DNA/topoisomerase complexes**
 - **Impaired mitochondria → increased ROS → lipid peroxidation + hepatocyte injury⁵**
 - **Hypothesis generating, not definitive**

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