Hepatic Lymphoproliferative Lesions in the Setting of Chronic, Multi-Drug Immunosuppression

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Background

- Drug induced liver injury (DILI) may have an association with TNF-α inhibitors as multiple agents within the class have been implicated
  - Median latency period 13 weeks, but patients with autoimmune features had a higher latency of 16 weeks[1]
  - Good prognosis with drug discontinuation, may also benefit from course of corticosteroids
- In one study, 8 of 11 of patients with DILI went on to tolerate a different TNF-α inhibitor without further liver injury[2]
- Increased incidence of lymphoma in patients with rheumatoid arthritis (RA) on adalimumab, when compared to RA patients not on any TNF-α inhibitors[3]
  - Standardized mortality rate indicates that no more deaths occurred in RA patients taking adalimumab than in the general population[4]

Introduction

Disease modifying anti-rheumatic drugs (DMARDs), target the immune system to reduce inflammation and prevent disease progression. This predisposes patients to infections and other rarer adverse events, like the following case of hepatic lymphoproliferative lesions.

"I am still fighting in my mind the fear of the cancer scare."

--Patient response when asked about trying a new DMARD

Case Description

Patient: 61-year-old African American man with RA presents for a GI consult due to abdominal pain and recent weight loss (230→200lbs)

RA Meds: adalimumab 40mg/0.8mL inj., prednisone

Previous RA Meds: methotrexate (1yr), etanercept/leflunomide (10yrs+), sulfasalazine (1yr), prednisone (15yrs+)

Family History: Lung cancer (father, heavy smoker)
Social History: Denies tobacco, alcohol, and drug use
Pertinent ROS: Denies fevers, chills, and night sweats

Pertinent Labs:
AFP, CEA, and liver enzymes within normal limits
Hepatitis B and C negative

Work-Up Timeline

November 2018	Incidental liver lesions found on CT
May 2019	Repeat CT and biopsy #1
August 2019	Biopsy #2
March 2021	Colonoscopy/EGD
July 2021	Repeat CT shows progression of lesions (Fig. 1A)
August 2021	Biopsy #3 (Fig. 1B, 1C)
September 2021	Adalimumab stopped
October 2021	PET scan unremarkable
February 2022	CT without lesions

Biopsy Results

Biopsy #1	Biopsy #2	Biopsy #3
Cytologic atypia	No signs of malignant cells	Cytologic atypia
Necro-inflammatory injury w/ multiacinar collapse	Benign hepatic parenchyma	Atypical lymphoid infiltrate, suspicious for B cell lymphoproliferation
CD20+ CD3, CD5, CD43+ CD15-	CD34-	CD20+ BCL6, Cyclin D1- CD23-

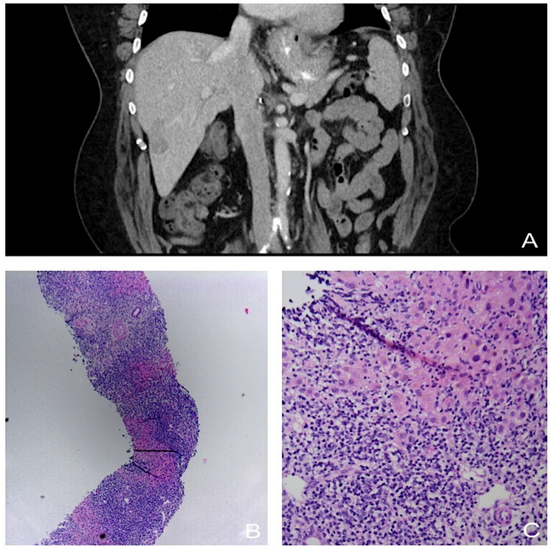

Figure 1. (A) Liver CT from 2021 depicting an enlarging, hypodense lesion (B) Liver biopsy H&E stain, 4x (C) Liver biopsy H&E stain, 20x

Discussion

This patient had an estimated 20-year pharmacologic treatment history with TNF-α inhibitors. He spent most of those years on etanercept, but adalimumab is the agent thought to have caused the hepatic lymphoproliferation due to the regression of the lesions once it was discontinued. It is recommended to provide a short-term course of corticosteroids to treat DILI, begging the question of whether this patient's long term prednisone use provided a buffer to the toxic effects of the TNF-α inhibitors.

Biopsy #1 results showed inflammatory injury as well as large and irregular lymphoid cells, but the pathology report indicated no concern for neoplasm or lymphoproliferative process. Additional biopsy was recommended only if there was a strong clinical correlation.

Biopsy #3 results strongly favor the differential of a lymphoproliferative lesion, rather than a cirrhotic or inflammatory etiology. With the discontinuation of adalimumab these lesions resolved, reminiscent of the resolution of a DILI.

Conclusions

Physicians who manage autoimmune disease by prescribing biologic therapy, especially TNF-inhibitors, must be vigilant of the risk of liver injury and lymphoma.

It is important to maintain clear communication with the patient in the case of any complications to strengthen the physician-patient relationship and avoid future noncompliance.

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