

Background

- Drug-induced autoimmune hepatitis (DIAIH) is a pathologic immune response against proteins in the liver triggered in susceptible individuals by drugs or herbal remedies¹
- While any supplement can cause idiosyncratic hepatotoxicity, up to 16% of drug-induced liver injuries are attributable to over-the-counter supplements¹
- There are limited data on herbal medicine-related hepatotoxicity, leading to underreporting in registry tools, such as NIH LiverTox, which are important for disease recognition and clinical management
- This topic is particularly understudied in pregnant patients, with most current clinical information coming from case reports.
- While use of supplements is common during pregnancy, there is limited information regarding their safety and impact on both maternal and fetal health

Case Presentation- History of Present Illness

HPI:

A previously healthy G4P2A1 28-year-old presented at 5 weeks of pregnancy with right upper quadrant pain and fevers

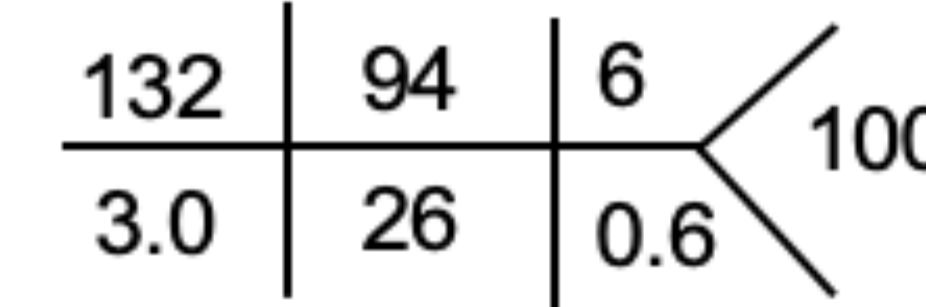
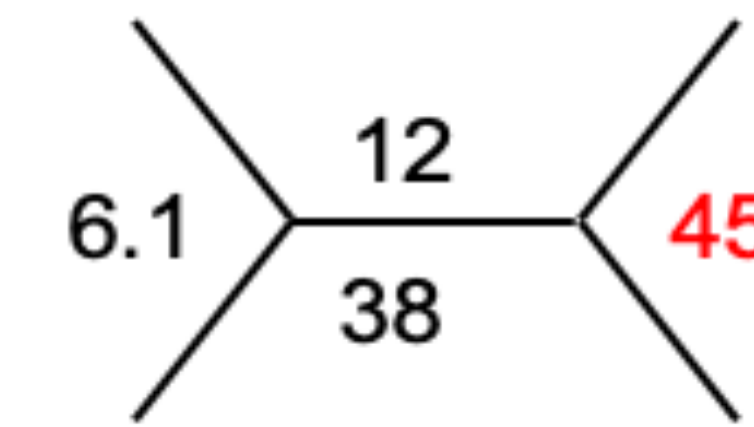
- Patients prior 2 pregnancies complicated by intrahepatic cholestasis of pregnancy requiring early delivery at 38 weeks
- Initial labs demonstrated hyperbilirubinemia and severe transaminase elevation
- Viral hepatitis panel negative and acetaminophen level undetectable
- MRCP revealed thickened gallbladder wall with normal intrahepatic ducts and normal common bile duct consistent with cholecystitis
- Patient presumed to have acute cholecystitis and underwent laparoscopic cholecystectomy
- Despite this procedure, liver enzymes continued to worsen and she developed signs of synthetic dysfunction requiring transfer to University of Colorado Hospital for further evaluation

Physical Exam Upon Transfer:

- BP 92/52, P 96, T 38.8 C, R 20
- A&O x3, no focal
- No asterixis
- Scleral Icterus and jaundice**
- Abdomen soft, non-distended, non-tender to palpation, well healing scars in RUQ
- Rash (blanching, diffuse, covering most of BSA) - see image 2**

Objective Data

- AST 2893
- ALT 2664
- TBili 2.6
- Alk Phos 460
- INR 1.3



- Hepatitis serologies negative for: acute HAV, HBV, and HCV.
- EBV, CMV antibodies negative.
- HSV PCR negative.
- APAP undetectable
- Laboratory evidence of AIH: ANA +, Anti-Mi+ 34.5 (ref < 25), U1-RNP/RNA-A68 2.4, Chromatin Abs 1.6

Pathology

Image 1 Liver biopsy showed acute-on-chronic hepatitis with an abundance of plasma cells (A) and dense portal inflammation (B) most consistent with autoimmune hepatitis v DILI.⁶

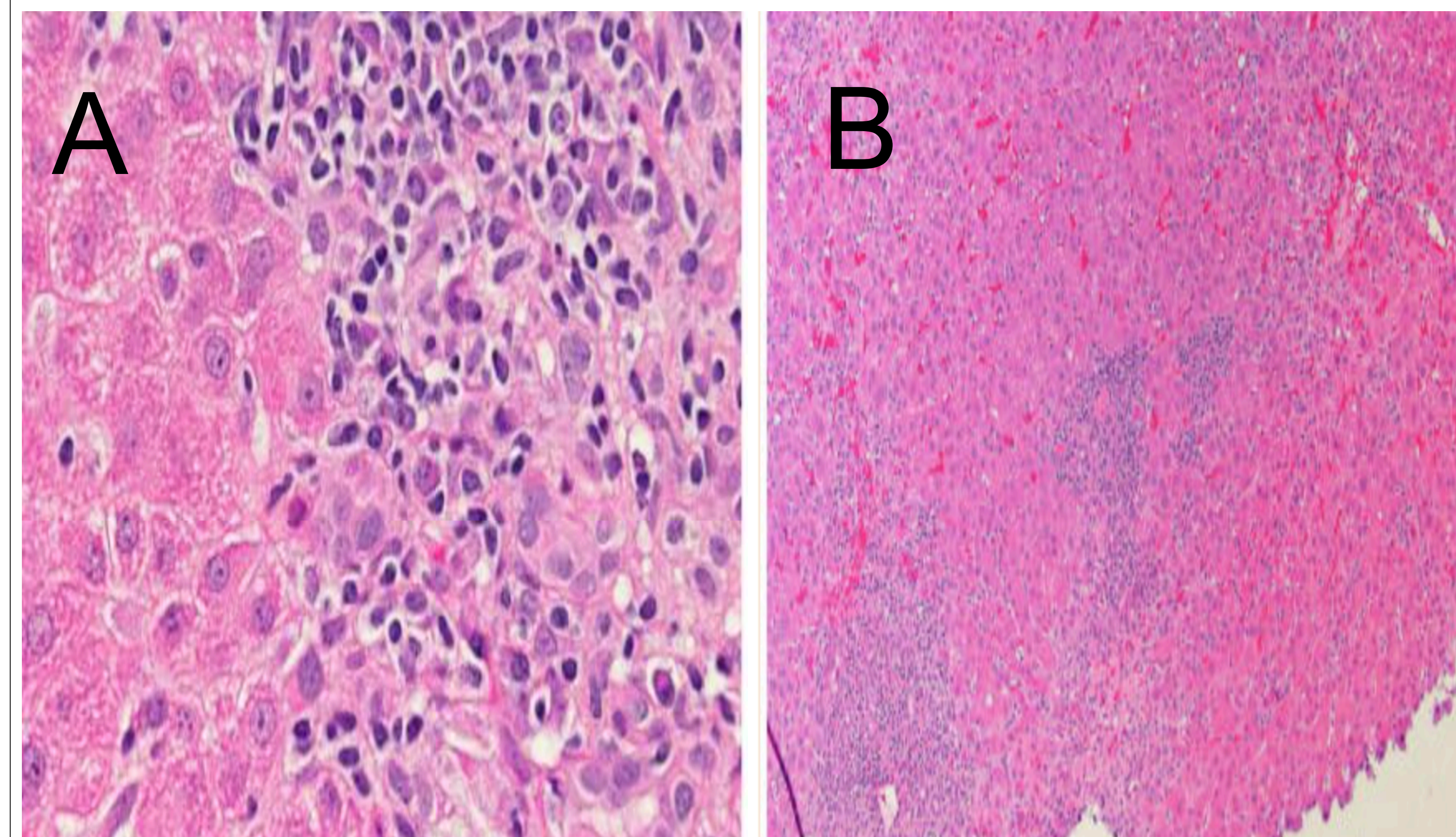
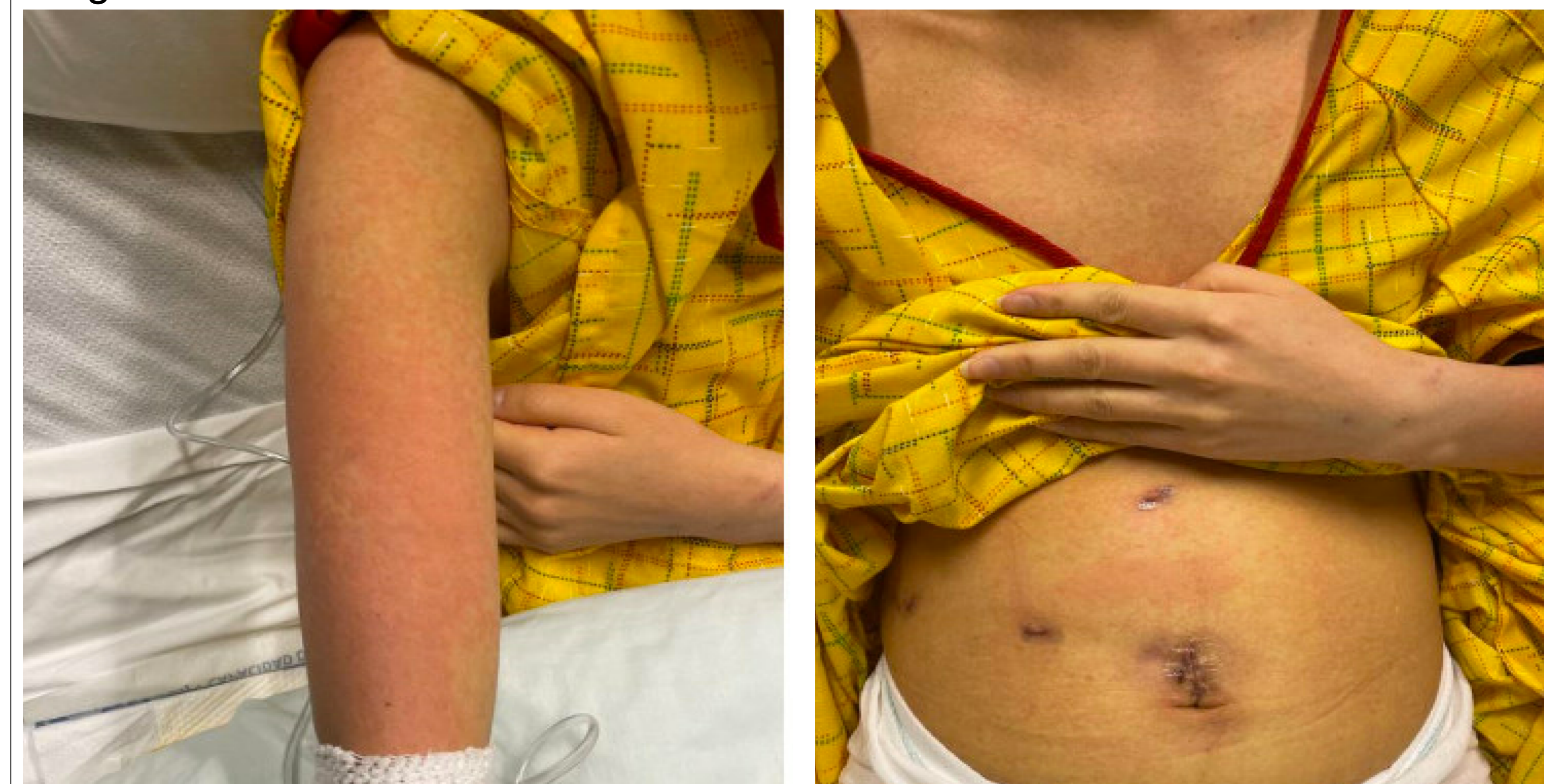


Image 2 Diffuse blanchable rash



Clinical Course

- Serology and pathology results demonstrated evidence of autoimmune hepatitis (AIH) with possible drug-induced liver injury
- Prior to admission, patient had started taking herbal supplement HemoHIM with purported immune support; thought to be possible driver of liver injury
- As AIH often presents during pregnancy, unclear if this presentation represented DIAIH or AIH
- Patient started on 60 mg prednisolone with subsequent clinical and laboratory improvement
- Despite maternal improvement, the patient suffered spontaneous abortion early in the treatment course
- Given concern for possible AIH and sluggish normalization of LFTs, started on azathioprine but self-discontinued after 7 months.
- Liver enzymes remained stable off azathioprine and was thus not restarted

Discussion

- Current estimates report DIAIH accounts for 2-18% of AIH cases^{3,4} and 2.9-8.8% of DILI³
- This case demonstrates the diagnostic challenges of DIAIH in prenatal patients
- DIAIH lacks pathognomonic features distinct from AIH given similar autoimmune serologic profiles and pathological features³
- There is an absence of specific diagnostic criteria and no consensus on the adequate terminology for the various clinical patterns of DIAIH⁴
- Some important distinguishing factors in AIH v DIAIH include:
 - Immuno-allergic presentation with skin rash, fever, lymphadenopathy, and eosinophilia favor DIAIH, as it may occur in up to 30% of DIAIH⁴
 - Frequently, DIAIH resolves with discontinuation of the offending agent. However, if there is no clinical improvement, steroids with or without immunosuppressive agents are often started (as seen in this case)
 - In general, DIAIH requires a significantly shorter treatment course with steroids than does AIH to achieve remission (2 mo vs 16.8 mo)⁵

References:

- Zucker, Kelly DO¹; Fung, Brian M. MD¹; Haddad, Nael MD²; Mehta, Shivang MD¹ The American Journal of Gastroenterology: October 2021 - Volume 116 - Issue - p S1102 doi: 10.14309/01.ajg.0000784032.10708.6a
- Kamath P, Kamath A, Ullal SD. Liver injury associated with drug intake during pregnancy. *World J Hepatol.* 2021;13(7):747-762. doi:10.4254/wjh.v13.i7.747
- de Boer YS, Kosinski AS, Urban TJ, Zhao Z, Long N, Chalasani N, Kleiner DE, Hoofnagle JH Drug-Induced Liver Injury Network. Features of Autoimmune Hepatitis in Patients With Drug-induced Liver Injury. *Clin Gastroenterol Hepatol.* 2017;15:103-112.e2
- Mack CL, Adams D, Assis DN, Kerker N, Manns MP, Mayo MJ, Vierling JM, Alsawas M, Murad MH, Czaja AJ. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. *Hepatology.* 2020;72:671-722.
- Martínez-Casas OY, Díaz-Ramírez GS, Marín-Zuluaga JI, Muñoz-Maya O, Santos O, Donado-Gómez JH, Restrepo-Gutiérrez JC. Differential characteristics in drug-induced autoimmune hepatitis. *JGH Open.* 2018;2:97-104
- Kleiner DE. Recent Advances in the Histopathology of Drug-Induced Liver Injury. *Surg Pathol Clin.* 2018 Jun;11(2):297-311. doi: 10.1016/j.path.2018.02.009. PMID: 29751876; PMCID: PMC5953206.