Vanishing Tacrolimus Syndrome

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Introduction

We present this case because cellular rejection is common in transplanted livers and therapeutic immunosuppressant (IS) levels are needed to minimize this risk of rejection. This case stresses the need to fully explore, and potentially reexplore common causes of subtherapeutic IS levels.

Patient Presentation

- 38-year-old man, with a medical history notable for alcohol related cirrhosis and liver transplant in 2019, followed by 2 episodes of acute organ rejection.
- Presented with 1 week of generalized abdominal pain, chronic diarrhea of 10-15 stools daily, pruritis, and nausea. similar to previous hospitalizations for organ rejection.
- Denied fevers, chills, recent travel, diet changes, alcohol use, denied blood or mucus in stools, denied weight loss
- Reported medication compliance

Exam on Presentation

T 36.6 C, BP 133/78, HR 77, RR 18, SpO2 98%

General: Well nourished, appears anxious and uncomfortable.
HEENT: No scleral icterus
Cardiovascular: RRR, no murmurs. No JVD.
Respiratory: Clear to auscultation bilaterally.
Abdomen: generalized abdominal pain
Skin: No rashes or lesions, no jaundice
Extremities: No edema.
Neuro: Alert and oriented x3, no asterixis

Labs

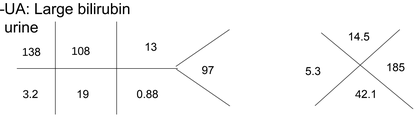
-C. diff PCR: negative
-COVID negative
-RSV negative
-Norovirus negative
-Influenza A and B negative
-Enteric panel: negative

Alk Phos 538 U/L
ALT 714 U/L
AST 784 U/L
Tbili 11.9 mg/dL
Direct bili 9.4 mg/dL
Albumin 3.5
Total protein 7.6
INR 1.03
PTT 29seconds

Tacrolimus level <1.0

-EBV serology negative
-CMV serology negative
-HSV serology negative
-IgA 267
-tTG IgA and IgG not elevated

-UA: Large bilirubin urine



Clinical Course

- Since transplant in 2019, had subtherapeutic tacrolimus levels and he had been treated with IV steroids, prednisone, sirolimus, increased doses of tacrolimus, and addition of fluconazole (for cytochrome (CYP) inhibition) during multiple hospitalizations and outpatient follow ups. Had also been treated with azathioprine and belatacept (on 5/27, 5/31, and 6/10) to help against transplant rejection.

- Underwent liver biopsy on 5/27 showing changes of acute on chronic rejection with evolving ductopenic rejection.

- Patient presented with abnormal liver tests concerning for another episode of transplant rejection on 6/6.

- Started on IV Tacrolimus on 6/6 with immediate increase in tacrolimus levels.

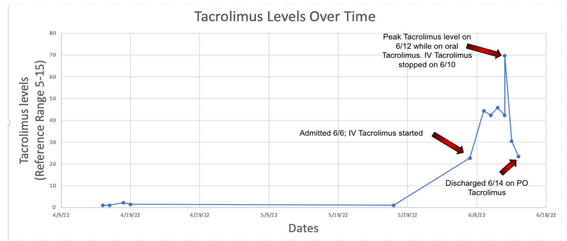


Figure A. Tacrolimus level over tie on oral and IV therapy

- Work up for infectious causes of diarrhea and elevated liver enzymes were negative.

- With concern for possible malabsorption, underwent workup with EGD on 6/7 and colonoscopy 6/8 with biopsies. Both were negative for malabsorptive pathologies. Colonic biopsies showed increased crypt epithelial apoptosis, non specific.

- With concern for pancreatic insufficiency, fecal elastase and fecal fat levels were obtained, which were within normal limits.

- IV tacrolimus stopped on 6/10 due to high levels. Patient was started on pancreatic enzymes and transitioned to oral tacrolimus on 6/11. Peak level 6/12 showed evidence of absorption. Level 23.1 on day of discharge. Fluconazole booster discontinued. Discharged on 5mg BID.

- LFTs improved with detectable tacrolimus levels, but not yet normal at discharge.

- Pruritis secondary to cholestasis also improved and discharged with increased Zoloft dose and ursodiol was added.

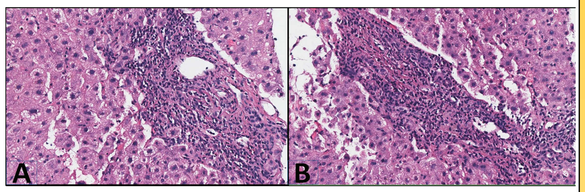


Figure B. Liver biopsy (panels A&B, hematoxylin & eosin stain) showing marked portal infiltrate and other features of cellular rejection.

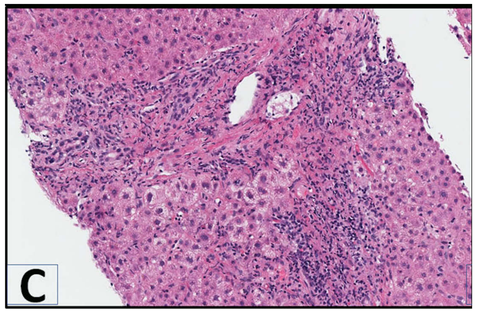


Figure C: After initial treatment, repeat biopsy (panel C, hematoxylin & eosin stain) shows less inflammation but still significant. Not seen in the earlier biopsy is onset of duct senescence and focal loss.

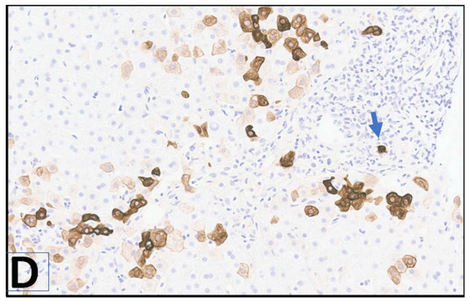


Figure D. The CK7 stain in panel D demonstrates a portal tract in which the bile duct is represented by a single residual epithelium (blue arrow). (Original magnifications: panels A, B & D: 200x; panel C: 100x)

Post Discharge

- Ongoing diarrhea and undergoing additional workup with ddx including: pancreatic insufficiency vs some other etiology malabsorption vs s/e medications vs continued mycophenolate toxicity vs SIBO vs long COVID-related IBS vs small bowel tumor (hormone secreting or otherwise) vs hyperthyroid vs other.
- Ongoing pruritus with increasing total bilirubin levels (last at 23)
- Tacrolimus increased to 10mg BID given concern for ongoing rejection. Additionally, continues to be on prednisone, azathioprine, and belatacept.

Discussion

- Rejection is the most usual cause of primary dysfunction of liver allograft transplants. Acute rejection has an incidence of 12%-19%, and chronic rejection is less usual (2.5%-17%) and irreversible.[4]

- The incidence of acute and chronic rejection has declined with improvement of immunosuppression regimens in liver transplant recipients.[3]

- Incidence of rejection can be increased due to subtherapeutic drug levels. Causes of such include drug inhibition[1], malabsorption, medication non-compliance.[2]

- Strategies such as CYP inhibition can be applied to increase immunosuppression availability. Immunosuppressants can be combined to achieve therapeutic levels.[3]

Learning Objectives

- It is important to think broadly and consider various causes of subtherapeutic drug levels in transplanted patients; considering malabsorption causes, drug metabolism, enzyme deficiencies, and medication compliance.
- This case also stresses the importance of collaborative efforts in patient care, as different physicians have participated in trying to understand the etiology of the patient's medical issues.

References

[1]Baciewicz AM, Baciewicz FA Jr. Cyclosporine pharmacokinetic drug interactions. Am J Surg. 1989 Feb;157(2):264-71. doi: 10.1016/0002-9610(89)90541-2. PMID: 2644865.

[2]Choudhary NS, Saigal S, Bansal RK, Saraf N, Gautam D, Soin AS. Acute and Chronic Rejection After Liver Transplantation: What A Clinician Needs to Know. J Clin Exp Hepatol. 2017 Dec;7(4):358-366. doi: 10.1016/j.jceh.2017.10.003. Epub 2017 Nov 7. PMID: 29234201; PMCID: PMC5715482.

[3]Di Maira T, Little EC, Berenguer M. Immunosuppression in liver transplant. Best Pract Res Clin Gastroenterol. 2020 Jun-Aug;46-47:101681. doi: 10.1016/j.bpg.2020.101681. Epub 2020 Sep 11. PMID: 33158467.

[4]González JT, Bellido CB, Riera GJ, Marente VC, Gómez LM, Artacho GS, Martínez JM, Díez-Canedo JS, Ruiz RJ, Bravo MA. Study of liver transplant rejection in alcoholism-induced cirrhosis. Transplant Proc. 2013;45(10):3650-2. doi: 10.1016/j.transproceed.2013.10.023. PMID: 24314985.