Drug Induced Liver Injury Cases

Case #1

A.S., a16 year-old female, was found by her pediatrician to be slightly jaundiced during a routine school physical. She denied any history of liver disease, abdominal pain, alcohol use or abdominal trauma. Lab evaluation showed a moderately elevated bilirubin of 2.3 mg/dL (0.3-1.0 mg/dL) along with an ALP and GGTP concentration of about 4 times normal. Her AST was 23 IU/L (8-42 IU/L).

A.S. denied being on any medications (except for vitamins), taking illicit drugs or being exposed to toxins. Nothing suggested the possibility of neoplastic or infectious process (temperature of 98.9 °F [37.2°C] and white blood cell [WBC] count of 7.5 $x10^3$ cells/mm^3 [4.8-10.8 x 10^3 cells/mm^3]. Ultrasound of the liver and biliary system was normal, with no evidence of biliary dilation.

The patient's parents then took her to a pediatric hepatologist. After much discussion (and threat of a liver biopsy), A.S. tearfully revealed that she had gone to a local family planning clinic and was using birth control pills.

Questions:

1. Based on A.S.'s labs and presentation, what type of liver injury would you classify her as experiencing?

2. What was the importance of the ultrasound?

Case #2

A 22 year old man with systemic lupus erythematosus with polyserositis and nephritis was started on high doses of prednisone to which azathioprine was added in an initial doses of 50 mg daily, later increasing to 100 mg daily. Three weeks later, serum ALT and alkaline phosphatase levels, which had been normal, began to rise and a week later he became jaundiced (Table). Physical examination showed no evidence of chronic liver disease. Tests for hepatitis A and B and CMV infection were negative. Serum autoantibodies had decreased during the month of immunosuppressive therapy. Azathioprine was stopped promptly, but liver tests worsened for

the next week. A liver biopsy showed marked cholestasis and centrolobular ballooning degeneration with an occasional acidophil body, but scant inflammation and no fibrosis. Liver tests subsequently began to improve and were normal 6 weeks later.

Time After Starting Drug	Time After Stopping Drug	ALT (U/L)	Alk P (U/L)	Direct Bilirubin (mg/dL)	Other
0		25	75	0.0	
1 week		105	80	0.2	
3 weeks		110	90	0.1	
3.2 weeks	0 weeks	705	290	1.2	Admission
4.5 weeks	1 week	530	550	4.8	Liver Biopsy
6 weeks	3 weeks	350	410	0.2	
7 weeks	4 weeks	180	290	0.3	
9 weeks	6 weeks	40	95	0.1	
Normal Values		**<50**	**<100**	**<0.3**	

1. At what time point do the patient's liver function tests suggest the presence of liver injury?

2. Calculate R for that day. Based on the result, how would you classify the type of liver injury the patient is experiencing?

3. At 3 weeks after stopping the drug, what is R now? Based on this number how would you classify the type of liver injury?

Case #3

A 33 year old woman was treated with a 21-day course of sulfamethoxazole/trimethoprim (TMP-SMZ) (80 mg/400 mg) for sinusitis. One day after stopping therapy she developed a macular rash, fever, right upper quadrant abdominal pain and nausea. Three days later she was seen in an emergency room, found to have fever, rash and systemic symptoms, and was hospitalized (Table). She had elevations in ALT and alkaline phosphatase, but serum bilirubin levels remained in the normal range. She had no history of liver disease, high risk behaviors, or exposures to viral hepatitis. She drank little alcohol (1-2 drinks per week) and took no other medications except for multivitamins and an occasional ibuprofen. Blood counts were normal except for mild eosinophilia (7%). Tests for hepatitis A, B and C were negative as were autoantibodies. Ultrasound of the liver was normal without gallstones. Her fever and rash resolved and she was discharged with a diagnosis of sulfonamide hypersensitivity reaction. Liver tests fell into the normal range within 4 weeks on onset of symptoms.

Time After Starting Drug	Time After Stopping Drug	ALT (U/L)	Alk P (U/L)	Direct Bilirubin (mg/dL)	Other
25 days	4 days	981	195	0.5	Hospitalization
26 days	5 days	805	213	0.8	Normal ultrasound
27 days	6 days	623	306	1.1	Discharged
5 weeks	12 days	156	386	0.6	Asymptomatic
6weeks	3 weeks	49	168	0.4	
9 weeks	5 weeks	34	77	0.4	
Normal Values		**<45**	**<130**	**<1.2**	

1. On presentation, what type of liver injury is the patient experiencing?

2. What features of the case are supportive of sulfamethoxazole/trimethoprim causing an idiosyncratic hypersensitivity reaction in this patient?

3. Can sulfamethoxazole/trimethoprim be prescribed to this patient in the future?

Case #4

Among 218 patients with latent tuberculosis (positive tuberculin skin test) treated with a one year course of isoniazid, 8 developed elevations in both AST and bilirubin, but none developed clinically apparent hepatitis. The course of AST and bilirubin elevations from two patients (table 4 from the publication: Cases 1 and 2) are shown.

Weeks After Starting Drug	Case #1 AST (U/L)	Case #1 Bilirubin (mg/dL)	Case #2 AST (U/L)	Case #2 Bilirubin (mg/dL)
0	16	0.3	19	0.5
4	135	0.9	35	0.4
8	663	5.2	37	0.4
12	412	3.6	49	0.4
16	78	1.2	92	0.4
20	37	1.4	181	0.6
20	29	1.1	342	0.6
24	29	1.1	342	0.6
28	22	1.2	920	4.9
32	22	1.3	201	1.8
40	20	0.6	77	0.6
48	18	0.9	124	0.7
52	15	0.8	138	0.6
After	17	1.3	62	0.6
Normal Values	**<30**	**<1.2**	**<30**	**<1.2**

1. Describe what is happening in these two cases to the patient liver values over time despite continuing isoniazid therapy. What phenomenon occurring?

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(Answers)

Case #1 (From Lee. Basic skills in interpreting laboratory data. 4th ed. Bethesda, MD; American Society of Health-System Pharmacists; 2009)
Discussion

1. Cholestatic. This case demonstrates that oral contraceptives, primarily because of their estrogen content, can cause alterations in cholestatic test results (manifested by an elevated bilirubin, GGTP, and ALP) with relatively normal aminotransferases.

2. The ultrasound helped to distinguish between intra- and extrahepatic cholestasis. The absence of biliary dilation suggested intrahepatic cholestasis. The normal AST suggested that jaundice was not due to hepatitis. Cholestasis from oral contraceptives is generally benign and reverses promptly when the medication is withdrawn

Case #2 (From http://livertox.nih.gov)

1. At 3.2 weeks. ALT >3 x ULN and Alk P >2 x ULN.
2. At 3.2 weeks, R=4.8, suggesting mixed liver injury
3. R=1.7, suggesting cholestatic disease

Key Points
Medication: Azathioprine (50-100 mg daily)
Pattern: Mixed (R4.8 initially, falling to 1.7)
Severity: 3 + (was not discussed during presentation. More information regarding severity grading available at http://.livertox.nih.org)
Latency: 3.5 weeks
Recovery: 6 weeks
Other medications: Prednisone, clonidine (0.2 mg twice daily); both continued

Discussion
This is a typical case of acute idiosyncratic liver injury caused by azathioprine. The initial serum enzyme pattern was indicative of mixed hepatocellular-cholestatic injury, but subsequently values were indicative of cholestatic hepatitis, which was supported by the finding of marked cholestasis with minimal inflammation by liver biopsy. The clinical course and presentation may have been altered by the concurrent use of high doses of prednisone (perhaps accounting for lack of eosinophils on liver biopsy). This syndrome appears to be more common with higher doses of azathioprine.

Case #3 (From http://livertox.nih.gov)

1. Hepatocelluar (R=14)
2. Fever, rash, eosinophilia, and systemic symptoms. Latency period for idiosyncratic hypersensitivity hepatotoxicity believed to be in the neighborhood of 1-6 weeks. Therefore the latency of 3 weeks is consistent.
3. No. The patient should be considered to have a severe allergy to sulfamethoxazole/trimethoprim that should be documented.

Key Points

Medication: Trimethoprim (80 mg)/Sulfamethoxazole 400 mg
Pattern: Hepatocellular R=14
Severity: 1+ (Anicteric) (was not discussed during presentation. More information regarding severity grading available at http://.livertox.nih.org)
Latency: 3weeks
Recovery: 4 weeks
Other medications: multivitamins, ibuprofen

Discussion

This patient had a typical, but mild immunoallergic hepatitis with fever, rash, constitutional symptoms, eosinophilia and ALT elevations, appearing within 3 weeks of starting TMP/SMX and resolving rapidly once it was stopped. Despite the height to the ALT elevations, the liver injury was mild, minimally symptomatic and not associated with jaundice or hepatic synthetic dysfunction. Some degree of ALT or alkaline phosphatase elevations is common in patients who have hypersensitivity reactions to sulfonamides and might be missed if blood testing is not done. The patient should be warned against future exposure to sulfonamides; with second exposures the liver injury can become more acute and more severe.

Case #4 (From http://livertox.nih.gov)

1. Despite developing evidence of liver injury with jaundice, these two patients continued therapy with isoniazid and recovered completely (#1) or partially (#2). This phenomena is known as adaptation or tolerance.

Key Points

Medication: Isoniazid (300 mg daily for 52 weeks)
Pattern: Hepatocellular (Alk P values not given)
Severity: 2+ (jaundiced, not hospitalized) (was not discussed during presentation. More information regarding severity grading available at http://.livertox.nih.org)
Latency: 4 and 16 weeks to elevations in AST
Recovery: 20 weeks despite continuation of isoniazid in one patient, and persistent in the second

Other medications: Not mentioned

Discussion

Serum aminotransferase elevations occur in 10% to 20% of patients treated with isoniazid for 1 year, but levels are usually minimally elevated and transient and are rarely (~10%) associated with symptoms. The aminotransferase elevations generally arise within the first 12 weeks of therapy, but can appear as late as 48 weeks. In up to 5% of patients, aminotransferase levels rise to at least 3 times the upper limit of normal and a proportion of these patients develop jaundice. It is prudent to stop therapy for any elevation of ALT or AST above 5 fold the upper limit of normal or for sustained values above 3 times the upper limit of normal, and certainly for any symptoms or appearance of jaundice. However, as shown in these two cases, "adaptation" and spontaneous recovery can occur even with fairly high aminotransferase elevations. The difficulty is that injury can be sustained and severe and result in acute liver failure. Furthermore, there are no reliable predictive features for recovery versus progressive damage. In this study, the laboratory testing was done in retrospect and results were not available until the study was over. Because the patients did not have symptoms of liver injury, therapy was continued.