Azathioprine causing cholestatic jaundice in a lupus nephritis patient: A case report and review of literature

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ABSTRACT

The systemic lupus erythematosus (SLE) is an autoimmune disease affecting predominantly females of reproductive age group. Pregnancy is advised only after a period of disease quiescence for at least six months. Azathioprine (AZA) and prednisolone are the immunosuppressants commonly used during pregnancy in lupus nephritis. Azathioprine causing cholestatic jaundice has been reported only a few times but none in a patient with lupus nephritis, pregnant or otherwise to the best of our knowledge. We present an interesting case of a young pregnant patient of lupus nephritis (LN) developing cholestatic jaundice in the third trimester, causing diagnostic dilemma between drug-induced jaundice and Intrahepatic cholestasis of pregnancy which resolved after withholding azathioprine. We should be aware of this uncommon adverse effect of this very commonly used drug in SLE patients.

Keywords: *Azathioprine, Cholestasis, Jaundice, Pregnancy, Systemic Lupus erythematosus.*

Azathioprine is a derivative of thioguanine, a purine-mimic antimetabolite. It has been extensively used in organ transplant and various autoimmune diseases. Use of azathioprine in pregnancy complicated by systemic lupus erythematosus (SLE) has limited data restricted to one cohort of 31 pregnancies. The authors reported favorable outcomes and, consequently, recommended azathioprine for the treatment of SLE/Lupus nephritis (LN) in pregnancy [1]. It along with prednisolone is the immunosuppressant of choice in pregnancy.

CASE REPORT

A 25-years-old female, an old case of lupus nephritis Class III + V with initial presentation as a nephrotic syndrome (anasarca, hypoproteinemia) which was diagnosed four years ago received Mycophenolate mofetil (MMF) and prednisolone as induction therapy achieving remission and was on same drugs in continuation phase with no relapse. As she expressed the desire for pregnancy, she was switched to azathioprine (AZA) from MMF six months prior to conception and she had no disease activity when she conceived one year ago.

Clinically, she had no cutaneous manifestations of SLE, pallor, pedal edema and her other general and systemic examination was unremarkable. Her investigations in the first month of pregnancy were haemoglobin-10.9 gm/dl, serum urea/creatinine-18/0.6 mg/dl, serum protein/ albumin-7.0/3.9 gm/dl, Urine routine and microscopic examination (RE/ME) showed no RBCs/ cast, 24 hour urinary protein – 310 mg, complement factor 3(C3) – 154 mg/dl (Normal – 90- 180), Complement factor 4(C4) – 34 mg/dl (Normal- 10-40), double-stranded DNA (dsDNA) – 10.8 IU/L (Normal <30), beta 2 glycoprotein and anticardiolipin antibody were within normal limits.

She was continued on AZA 100 mg/day, Prednisolone10 mg/day, Hydroxychloroquine 400 mg/day and Ecosprin 75 mg/day. During follow-up, she had poor weight gain and during anomaly scan on Ultrasound (USG), intrauterine growth retardation

Table 1: Investigations Chart

Day	32 wks (D-Day of admission)	D+5 (Delivery)	D+7 (Aza withheld)	D+14	D+21	D+28
Hb	9.2	9.4				
Bil (D/I)	5.6 (3.2/2.4)	11.8 (8.0/2.8)	18 (10.4/7.6)	10.2	4.6	1.5
AST	29	57	123	68	45	34
ALT	29	67	148	76	63	35
Alk PO4	178	210				
Serum Bile acids	40					
USG Abd	Normal hepato-biliary system					
C3	127					
C4	30.3					
dsDNA	10.3					
Peripheral smear	No evidence of hemolysis					
24 hrs urinary protein	510 mg/TV					

Table 2: Previously reported cases of azathioprine induced cholestatic Jaundice

Year	Case report / Series	Journal	No of patients	Indication	Onset of Jaundice after initiation	Diagnosis
1980	CR	Davis et al Postgraduate medical journal	1	Chronic active hepatitis	2 weeks	Clinical
1984	CR	Depinho et al Gasstroenterology	1	SLE	3 WKS	Clinical
1990	CR	Perini et al J Heart Transplant	1	Post cardiac transplant		Clinical
1991	CS	Sterneck et al, Hepatology	2	Liver transplant	2 & 9 wks	Clinical
2005	CR	Eisenbach et al Immunopharmaco Immunotoxic	1	DLE	3	Liver biopsy
2010	CR	Salem et al Pharmacy world science	1	Pemphigus foliaceous	3 weeks	Enzyme activity
2011	CR	Viju et al IJ pharmacology	1	Post Keratoplasty	2 weeks	Liver Biopsy
2014	CR	Chertoff et al BMJ	1	Myas Gravis	12 months	Enzyme
2017	CS	Bjornsson et al (5) J Clin gastro	12	IBD, autimmune,pulmonary	41 days (Median)	Liver biopsy + Clinical

(IUGR) was detected at 18 weeks with no other anomalies and pregnancy was continued with regular monitoring. She had no features of increased disease activity either clinically or by laboratory parameters during follow up. At 32-weeks, she developed insidious onset jaundice with itching and clay coloured stools. Clinically, she had icterus with no hepatomegaly. Her initial bilirubin was 5.6 mg/dl with slightly raised transaminases; (laboratory parameters are given in Table 1) giving a provisional diagnosis of intrahepatic cholestasis of pregnancy (IHCP).

Table 3: Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Don't Know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+1
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	0
TOTAL SCORE				**5**

Ursodeoxycholic acid (UDCA) was started with mild relief of itching. She had premature rupture of membranes on the 5th day following admission and delivered a low birth weight baby per vagina. As she had worsening jaundice even after delivery, her azathioprine was withheld with rapid resolution of hyperbilirubinemia. Her bilirubin normalized by three weeks after withholding AZA confirming the diagnosis of Azathioprine induced cholestatic jaundice. On follow-up, she has no disease activity with normal lab parameters (Bilirubin -0.6 mg/dl) or other complications and the child is doing well.

DISCUSSION

SLE primarily affects women during their reproductive years, a period of six months of quiescence is recommended as the activity at the time of conception is associated with poor outcomes [2]. Patients with SLE have higher complication rates in both mother and child like preterm labor, preeclampsia, eclampsia, infections, thrombosis, neonatal death and fetal growth restriction as in our patient [3]. The immunosuppressant drugs considered for use in pregnant lupus patients are corticosteroids, azathioprine, tacrolimus and cyclosporine [4].

AZA is considered the safest immunosuppressant in pregnancy [1]. AZA has been associated with four forms of hepatotoxicity, including mild, transient and asymptomatic rises in serum

aminotransferase levels, an acute cholestatic injury, and chronic hepatic injury markedby veno-occlusive disease or nodular regenerative hyperplasia that typically occursafter long term use [5]. It has been mentioned as a cause of cholestatic jaundice in pregnancy seen in post-transplant patients [6]. No reports are suggesting an increased risk of IHCP in lupus patients [7] which was a strong possibility in our case but bilirubin rarely rises above 6 mg/dl in IHCP [8]. AZA causing cholestatic jaundice is a rarity which has been reported in few case reports and series so far (Table 2).

The mean time for onset of jaundice varies from as less as few days and rarely exceeded six months in the largest case series [5], it was 8 months in our patient. Our patient had shown improvement immediately after stopping AZA with a resolution of jaundice and normalization of liver functions tests (LFTs) suggesting the role of AZA with high probability as in Naranjo Nomogram (Table 3). The other methods that can be used are measuring methylmercarcaptopurine levels [9] or the demonstration of the cholestatic pattern on liver biopsy. We didn't intend on doing a liver biopsy as there was a rapid resolution of symptoms, and methylmercaptopurine levels were not available at our center. There have been studies on azathioprine in pregnant lupus patients or but none mentions this complication [1, 10, 11].

CONCLUSION

To conclude, we want to highlight this uncommon complication of a very commonly used drug in lupus patients. One should be more vigilant of jaundice in a patient using azathioprine even after a long duration of use.

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