A CASE OF WILSON'S DISEASE PRESENTING WITH PERSISTANT HEMOLYSIS

ABSTRACT:

Wilson's disease is one the rare autosomal recessive disorders of copper metabolism due to mutation in ATP7B gene located in chromosome 13. The mutations of this gene cause accumulation of copper in different tissues such as brain, liver, and eyes. The clinical presentation usually reflects this tissue distribution and varies from asymptomatic patients to those with hepatic or neuro-psychiatric manifestations. . Here, we report an interesting case of Wilson's disease which presented with mild persistent hemolysis leading to pre hepatic and post hepatic jaundice. He also had hepatocellular jaundice due to liver injury.

KEYWORDS: *Wilson's disease, Coomb's negative hemolytic anemia, gall stones*

INTRODUCTION

Wilson's disease is one the rare autosomal recessive disorders of copper metabolism due to mutation in ATP7B gene located in chromosome 13[1]. This gene is expressed mainly in liver and its product is a copper transporting ATPase 'the Wilson ATP ase', which transports copper for incorporation into ceruloplasmin or excretion into bile depending on intracellular concentration of copper.

The mutations of this gene cause accumulation of copper in different tissues such as brain, liver, and eyes. The clinical presentation usually reflects this tissue distribution and varies from asymptomatic patients to those with hepatic or neuro-psychiatric manifestations. Persistant hemolytic anemia is an uncommon manifestation of Wilson's disease in adults. Inorganic copper accumulating in RBC causing damage to RBC membrane, accelerated oxidation of hemoglobin and inactivation of the pentose phosphate and glycolytic pathways are the proposed mechanisms for acute hemolysis[1]. Here, we report an interesting case of Wilson's disease which presented with mild persistent hemolysis leading to pre hepatic and post hepatic jaundice. He also had hepatocellular jaundice due to liver in

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CASE REPORT

A 23 year old gentleman presented with jaundice for 2 days. He had vague right upper abdominal pain, loss of appetite and an episode of vomiting. He revealed history of similar illness in his elder brother but medical records were not available. On examination, patient was pale, icteric and had mild non tender hepatomegaly.

Laboratory evaluation showed conjugated hyperbilirubinemia with transaminitis, Coomb's negative intravascular hemolytic anemia. Peripheral smear showed macrocytic anemia with adequate platelets. Investigations are shown in table. Ultrasound abdomen showed mild hepato-splenomegaly with a calculus and organized sludge in gall bladder (Fig.1). Repeated work up for common hemolytic anemias like osmotic fragility test, sickling test, hemoglobin electrophoresis were negative. Glucose 6 phosphate dehydogenase and pyruvate kinase enzyme levels were normal. Serology to hepatotropic viruses like hepatitis A, B, C, E was negative. Slit lamp examination revealed Keyser Fleisher ring in both eyes.

Comment [WU2]: anemia

Considering the positive family history and Keyser Fleisher ring, serum ceruloplasmin was sent, and was 48.03mg/dl, with elevated 24 hours urine copper of 413.28 mcg/day. Hence, a diagnosis of Wilson's disease presenting with hemolytic anemia was made and patient was started on Cap. Pencillamine 500mg twice daily. With effective chelation, the patient's Nazer's prognostic index fall from 10 to 5 and patient was discharged on pencillamine and multivitamin supplements.

On follow up, the patient was switched over to Tab Trientine 250mg thrice daily and Tab zinc 50 mg thrice daily as he was not tolerating pencillamine. Patient used to come for regular follow up, and he was symptomatically better except for the upper abdominal pain. He discontinued trientine due to financial constraints and continued Tab zinc 50 mg thrice daily.

Four years later, patient presented with severe right hypochondrial colicky pain following intake of grape juice. USG abdomen showed gallbladder calculi, and cholecystitis. Upper gastrointestinal endoscopy was normal, CT abdomen showed calculous cholecystitis. The patient was treated with antibiotics and advised cholecystectomy, but he was not willing for surgery and hence managed conservatively.

Two months later, he presented with similar complaints precipitated by intake of black raisins. Laboratory evaluation revealed neutrophilic leukocytosis, intra vascular hemolysis and transient elevation of pancreatic amylase and lipase. USG abdomen revealed gall bladder calculi and due to unwillingness of the patient for cholecystectomy he was managed conservatively.

Three months later, he presented with left sided pleuritic chest pain and chest X-ray revealed left sided pleural effusion. CT chest revealed moderate left sided pleural effusion with passive atelectasis in left lower lobe. USG guided diagnostic thoracentesis revealed exudative lymphocyte predominant pleural effusion. Pleural fluid ADA was 35.62 U/L, amylase was 22U/L, bilirubin was 7.2mg/dl. AFB smear and gene Xpert in pleural fluid were negative and malignant cytology was also found to be negative. USG abdomen showed calculous cholecystitis with fluid collection around. Magnetic resonance cholangiopancreatography showed calculous cholecystitis with perforated gall bladder, intraparenchymal collection in segment V of liver (Fig.2). The left sided exudative pleural effusion was considered as a reactive effusion secondary to gallbladder rupture and patient underwent open cholecystectomy. Following surgery, chest pain and pleural effusion resolved as demonstrated by repeat CT chest. The patient was discharged after 10 days with Tablet Zinc 50mg thrice daily and multivitamin supplements.

DISCUSSION

Wilson's disease earlier named as Wilson's hepatolenticular degeneration has a prevalence of 1:30000 with a much more genetic prevalence, and mean age of presentation is 26.1 ± 17.2 with earlier diagnosis in men[3, 4]. Thirty percent patients with the mutation are asymptomatic and are usually detected with family screening[5]. And in symptomatic, half of them present with both hepatic and neurological features and the remaining half present with pure hepatic or neuropsyciatric manifestations[5].

Hemolytic anemia or even fulminant hepatic failure as the initial presentation of Wilson's is frequent reported in young children and adolescents[5]. The bursting of copper laden lysosomes leading to release of large amounts of copper in blood, and as copper is loosely bound to albumin it attacks the RBCs plasma membrane resulting in Coomb's negative hemolytic anemia or sometimes acute hemolytic crisis. Serum ceruloplasmin levels may be an ineffective screening tool as it is a positive acute phase reactant, but urine copper levels are invariably high[5]. But persistent hemolysis despite chelation therapy is rather rare in Wilson's disease.

In this report, we present a young male with Coomb's negative intra vascular hemolytic anemia and hepatic jaundice with no signs of decompensation or fulminant hepatitis. He had a similar history in his brother, which was not evaluated. No other family members were affected. Since Wilson's is one of the common causes of hemolytic anemia in young adults and the patient had a positive family history, urine copper level was estimated which was found to be high and diagnosis was confirmed. The patient was immediately started on chelation with D-pencillamine and he responded promptly. Since the Nazer's prognostic index was less than 7 after chelation, he was advised optimal medical management.

On follow up, the patient had significant improvement in transaminitis, but low level of hemolytic anemia persisted as evidenced by anemia, unconjugated hyperbilirubinemia and persistently low haptoglobin. When the patient presented four years later he had pigmented gallstones and cholecystitis secondary to hemolysis. The patient typically reported that precipitation of each episode of hemolysis follows intake of fresh or dried grapes.

Two months later, he developed left sided exudative lymphocyte predominant pleural effusion probably secondary to gallbladder rupture. But the perforation was self-sealed and the patient was stable. The pleural effusion settled after cholecystectomy. The effusion could be bilothorx but it is more common on right side or bilateral. Unilateral left sided pleural effusion due to gall bladder pathology is exceedingly rare.

The patient is on regular follow up and he is continuing to have persistant low level of hemolysis with occasional crisis, and is on zinc therapy now.

CONCLUSION

Even though Coomb's negative intra vascular hemolytic anemia is a common presentation, our extensive literature search to look for the unusual manifestation of Wilson's disease with persistent low level hemolysis leading to formation of pigmented gall stones, gall bladder rupture and left sided exudative pleural effusion secondary to gall bladder pathology have not been reported yet.

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PARAMETERS	Normal values	On first admission	After 2 weeks	After 6 months	After 4 years- 2nd admission	On discharge	2 months after 2nd admission	3 months after 2nd admission	2 year follow up
Haemoglobin	13-17g/dl	8.4		7.6	7.3	7.6	7.9	7.4	9.1
Total count	4000-11000 cells/ mm^3	7600		6000	4600	7700	16400	8900	7600
MCV	80-100FL	107.6		115	104.6	104.4	97.5	102.1	89.2
MCH	27-32PG	38.2		41.6	35.9	34.4	31.1	35.4	28.9
MCHC	33-38g/dl	35.5		35.9	34.3	33	31.9	34.7	32.4
Platelet count	1-5-4.5lakh/mm^3	2.86		2.62	2.06	1.90	3.27	2.55	3.75
RDW	11.5-13.5%	16.4		10.9	16.6	16.8	19.4	15.2	22.7
ESR	0-10mm/1hr	12			10	13			
BUN	7-18mg/dl	8	9		8	8	6	10	
Serum Creatinine	0.7-1.3mg/dl	0.76	0.76		0.60-	0.58	0.7	0.66	
Serum Bilirubin	0-1mg/dl	71.7	17.2	7.1	17.4	5.3	8.4	10.3	6.1
Direct bilirubin	0-0.25mg/dl	46.86	13.41	0.38	8.20	1.82	1.01	1.77	1.79
Indirect bilirubin	0.2-0.8mg/dl	24.84	3.79	6.72	9.2	3.48	7.39	8.53	4.31
SGOT	0-46U/L	257	92	56	89	60	38	61	123
SGPT	0-49U/L	897	81	53	41	34	45	60	195
ALP	60-170U/L	1102	128	83	78	57	78	106	163
GGT	15-85U/L	310	29	25		43	20	29	98
Total protein	6.4-8.2g/dl	6.5	6.7	6.3	7.2	6.5	7.4	7.5	8.1
Serum albumin	3.5-5g/dl	3.1	3.7	4.4	4.9	4	4.1	4.5	4.4
Serum globulin	2.3-3.5g/dl	3.4	3	1.9	2.3	2.5	3.3	3	3.7
LDH	200-	919					491		

	400U/L								
Reticulocyte count	0,5-2.5%	13							
Serum haptoglobulin	40-200mg/dl	<10					<10		
Osmotic fragility test		Neg							
Serum amylase	0-57U/L			31	36		529		
Serum lipase	0-59U/L			25	21		321		
Coombs test		Neg							
PT INR		1.60	1.3		1.57	1.34			1.32

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Figure 1: USG abdomen showed calculous cholecystitis with fluid collection around.

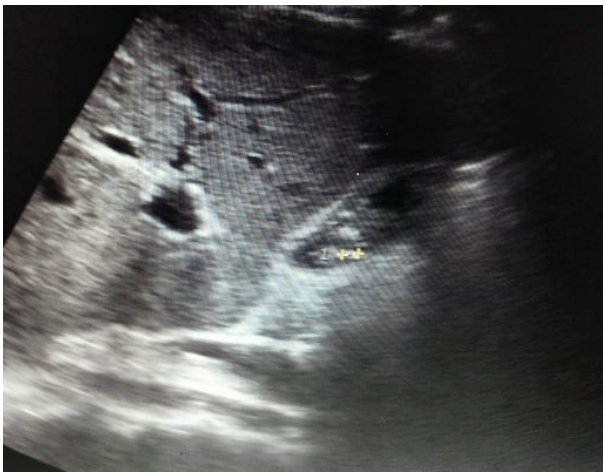

Figure 2: Magnetic resonance cholangio-pancreatography showed calculous cholecystitis with perforated gall bladder, intraparenchymal collection in segment V of liver