



Acute Hepatitis in Pregnancy: A Case Report

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Received date: 02 October 2020; **Accepted date:** 30 October 2020; **Published date:** 07 November 2020

Citation: Sarmento AMP, Oliveira ACT, Barbosa APXP, Campos CS, Porto JAS, Esteves LF, de Moraes LC, Vilano LS, Cerqueira MSM, Martins MC, Cerceau PS, Amaral PHS, Ferreira RRMS, Pires RA, Albuquerque RDV, de Souza SGTPG, Bertges ER, Panconi CR, Almeida FAMB, Zimmermann JB. Acute Hepatitis in Pregnancy: A Case Report. *Asp Biomed Clin Case Rep.* 2020 Nov 07;3(3):225-33.

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Abstract

Introduction: Several changes occur in women's body during pregnancy, as well as several pathologies can arise at this period, such as hepatitis. It is very important to have the correct diagnosis and proper treatment for pregnant women because liver diseases can increase maternal and/or fetal morbidity and mortality rates.

Case Report: Patient in the age group 32 years, G2P0A1, thrombophilic, using ASA, enoxaparin, folate, and B-complex, reported jaundice, low fever, and pruritus in the 32nd week of pregnancy. Laboratory exams showed high levels of direct hyperbilirubinemia and aminotransferases, with negative serology results for the most common viruses and autoimmunity markers. Hypervitaminosis B12 was an additional finding; it was canceled. The patient had a satisfactory recovery after support treatment.

Discussion: Hepatitis has several etiologies; it is caused by infections, medications, or triggered by the immune system. The main infectious agents causing hepatitis A, B, C, and E; Dengue, Zika, HTLV, cytomegalovirus, toxoplasmosis, rubella, and brucellosis were screened in the reported case - the patient was negative for all of them. Other possible diagnoses, such as acute liver steatosis of pregnancy, portal thrombosis, and autoimmune hepatitis were excluded. Hepatitis caused by medicines was not confirmed because clinical and laboratory exams showed improvement in the patient's clinical condition even with ASA and enoxaparin administration. The patient had high vitamin B12 level, which can be a liver damage marker. Transaminases and bilirubin showed a progressive decrease after the treatment; both patient and newborn had a satisfactory recovery. The reported condition was caused by a combination of factors, such as pregnancy hormone levels, unidentified infection, and possible predisposition to develop the disease. The patient remains under hematological and hepatological follow up, but there is no record of relapse, so far.

Keywords

Acute hepatitis; Autoimmunity; Hepatitis; Pregnancy; Vitamin

Introduction

Several changes occur in women's body during pregnancy as a way to ensure the availability of nutrients necessary for a healthy and sustained pregnancy. Several pathologies can arise at this period, including liver disorders exclusive to pregnancy or pre-existing ones, which can get worse during this time. It is very important to have the correct diagnosis and proper treatment for pregnant women because liver diseases can increase maternal and/or fetal morbidity and mortality rates [1].

Hepatitis in pregnant women depends on several factors; it can manifest in the acute or chronic form and lead to liver damage, failure, or liver cancer [2]. Intrahepatic cholestasis of pregnancy is the most common specific liver disease observed and the second leading cause of jaundice during pregnancy, with an estimated incidence rate of approximately 1/10,000 deliveries [3]. Pruritus, which can occur in up to 80% of cases, is its main symptom; other symptoms are jaundice, anorexia, general malaise, abdominal discomfort, choloria, and fecal acholia. Acute hepatic steatosis occurs in approximately 1/13,000 pregnant women, it is a potentially fatal pathology associated with 18% of maternal mortality and with 23% of fetal mortality [1,4]. Symptoms are unspecific and account for diagnosis delay. Nausea and vomit occur in 70% of cases, pain in the epigastrium, or right hypochondrium in 50%-80% of cases; flu-like symptoms are observed in some cases. Hellp Syndrome is a severe complication caused by preeclampsia; it is featured by hemolysis, elevated liver enzymes, and thrombocytopenia [1].

Viral hepatitis is one of the most common and potentially severe infections in pregnant women. It is the most common cause of jaundice during pregnancy and presents systemic manifestations. Acute hepatitis can affect pregnancy and, depending on the infectious agent, it significantly increases maternal and fetal mortality rates. Hepatitis A, B, C, D, or E viruses are the main etiological agents of hepatitis; however, even simple herpes can cause severe hepatitis. The initial

symptoms often meet those of infectious conditions such as malaise, fatigue, anorexia, nausea, and pain in the epigastrium or in the right hypochondrium. Hepatomegaly and jaundice are typical of disease evolution; it is important highlighting that virus type determines the likelihood of having a chronic disease. Pregnant women with viral hepatitis need to follow-up to control encephalopathies, coagulopathies, progressive weakness, and fulminant hepatitis (which are closely related to infection caused by the E virus) [5]. Accordingly, one can observe cases of autoimmune hepatitis, which is featured by chronic hepatocellular inflammation caused by the action of circulating autoantibodies that mainly affect women at childbearing age. Pregnancy brings along an immunosuppression state that can control clinical manifestations. However, it is possible having severe malaise, anorexia, fatigue, weight loss, and acute liver failure crises with jaundice, ascites, and coagulopathies [6-8]. Drug-induced hepatitis can also happen during pregnancy and lead to adverse effects. It is a severe inflammation caused by prolonged medication use, which results in acute hepatitis or fulminant hepatitis (in most cases, asymptomatic). Two mechanisms can generate drug-induced hepatitis: toxicity or idiosyncrasy. Toxicity derives from the intake of a substance that damages liver cells and causes hepatitis, at greater or lesser severity, depending on the ingested dose. In the case of idiosyncrasy, intrinsic factors cause liver injuries and affect individuals' susceptibility; however, it does not depend on the amount of medication taken. Clinical symptoms include nausea, vomit, malaise, acute liver failure, or fulminant liver failure (in severe cases) [9-11]. **Table-1** shows the main causes of hepatitis.

Authors of the current research herein report the case of a patient who developed severe hepatitis during pregnancy, her evolution, and support treatment.

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Patient, aged 32 years, G2PoA1, thrombophilic (acquired thrombophilia - antiphospholipid syndrome + MTHFR + protein S deficit) and history of fetal

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Table-1: Prenatal Exams			
Laboratory exam	Quarter		
	First	Second	Third
Hemoglobin (g/dl)	13.6	11.2	11.8
Hematocrit (g%)	33.3	33.1	35.1
Normal Lymphocytes (%)	31.1	32.2	31
Platelets (x1000)	165	145	205
Glucose	93	63	91
Dextrosol 75g	Gestational Diabetes		
Syphilis	N	N	N
Hepatitis C	N	N	N
HIV	N	N	N
Urinalysis	N	N	N
Vitamin D	32.3	37.7	39.4
Vitamin B	454	-	2000
Ferritin	41.6	35.7	38.1
Free Thyroxin	0.87	0.94	1
Thyretrophic Hormone	2.2	2.3	1.5
Toxoplasmosis	Immune		
Rubella	Immune		
Hepatitis B	Immune		
Cytomegalovirus	Immune		
Ultrasound exam			
First Quarter	Gestational age: 11 weeks, nuchal translucency= 0.9 mm		
Second Quarter	Gestational age: 23 weeks, normal fetal morphology, normal uterine doppler (pulsatility index); fetal weight: 566 g		
Third Quarter	Gestational age: 32 weeks, normal uterine doppler (pulsatility index), normal umbilical Doppler, fetal weight: 1873g, normal amniotic fluid, placentae grade 0		
	Gestational age: 36 weeks, fetal weight: 2879g, normal amniotic fluid, placentae grade and normal umbilical Doppler		

death, taking ASA (100 mg on a daily basis), enoxaparin (40 mg on a daily basis), folic acid and B-complex replacement, under follow-up with hematologist and obstetrician.

She started prenatal care at the 12th week of pregnancy and had satisfactory evolution up to the

31st/32nd weeks when she reported to prenatal care appointment with malaise, fatigue, low fever (for one week), jaundice, and mild pruritus throughout the body. **Fig-1** shows the patient clinical evolution during prenatal care based on gestational age. **Table-1** shows usual prenatal laboratory and ultrasound examination results and **Table-2** presents the laboratory and image

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exams performed during jaundice. **Fig-1, Fig-2** and bilirubin, respectively. **Fig-3** depict clinical evolution, transaminases, and

Table-2: Patient's laboratory and image exam		
Infections	Hepatitis A	Immune
	Hepatitis B	Immune
	Hepatitis C	Negative
	Hepatitis E	Negative
	Parvovirus	Immune
	Zika virus	Negative
	Dengue virus	Negative
	HTLV virus	Negative
	Measles	Negative
	Toxoplasmosis	Immune
	Rubella	Immune
	Cytomegalovirus	Immune
	HIV	Negative
	Syphilis	Negative
	Urine	Negative
Autoimmunity	Brucellosis	Negative
	ALKM antibody	Negative
	Antimitochondrial antibody	Negative
	Immunoglobulin IgG	Negative
	Anti-TPO antibody	Negative
	Complement C3	0.98
Others	Complement C4	0.28
	Seric alpha-1 antitrypsin	325
	Ceruloplasmin	70
	Zinc	81.3
	Vitamin C	0.54
	Vitamin B12	2000
	Copper	96.8
	Creatinine	0.74
	Folic Acid	24
	Alkaline phosphatases	50
	Amylase	38
Lipases	164	
Abdominal ultrasound	No signs of steatosis	

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Doppler ultrasound of portal system	Hepatic artery unobstructed, with normal blood flow. IR= 0.73
	Hepatic veins with three-phase flow pattern
	Superior mesenteric vein with normal caliber and hepatopetal flow of 21 cm/s
	Absence of collateral circulation or unobstructed

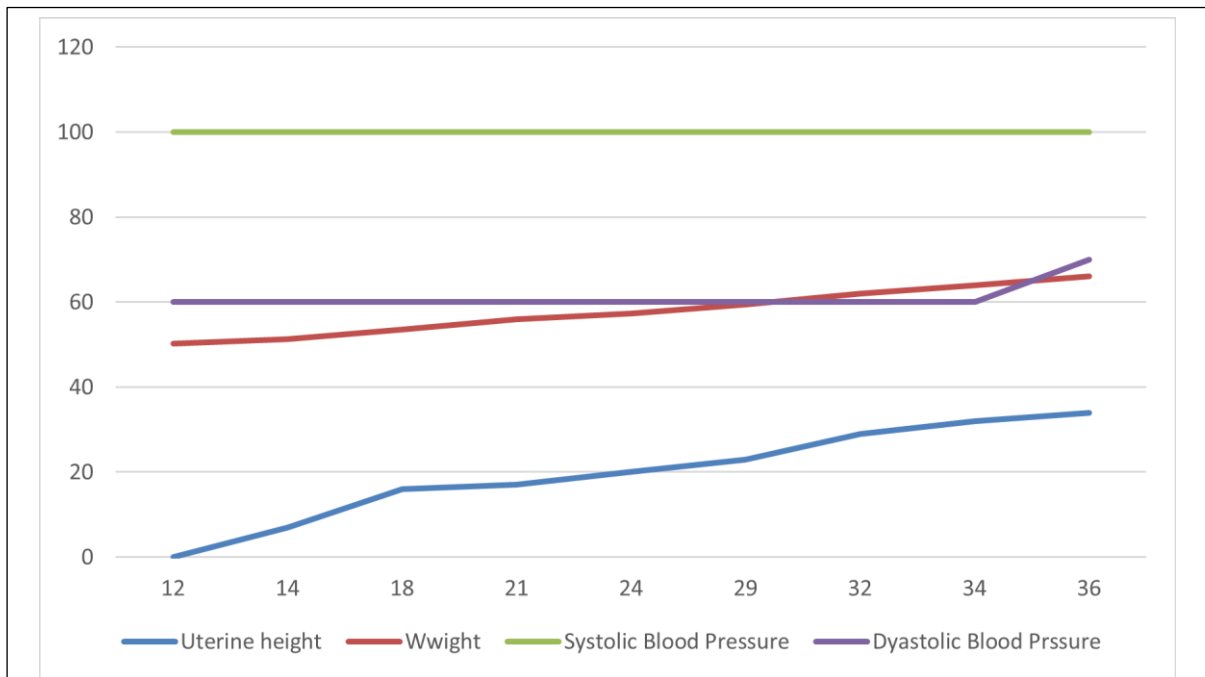


Fig-1: Evolution of patient's weight (kg), uterine height (cm) and blood pressure (mmHg) based on gestational week.

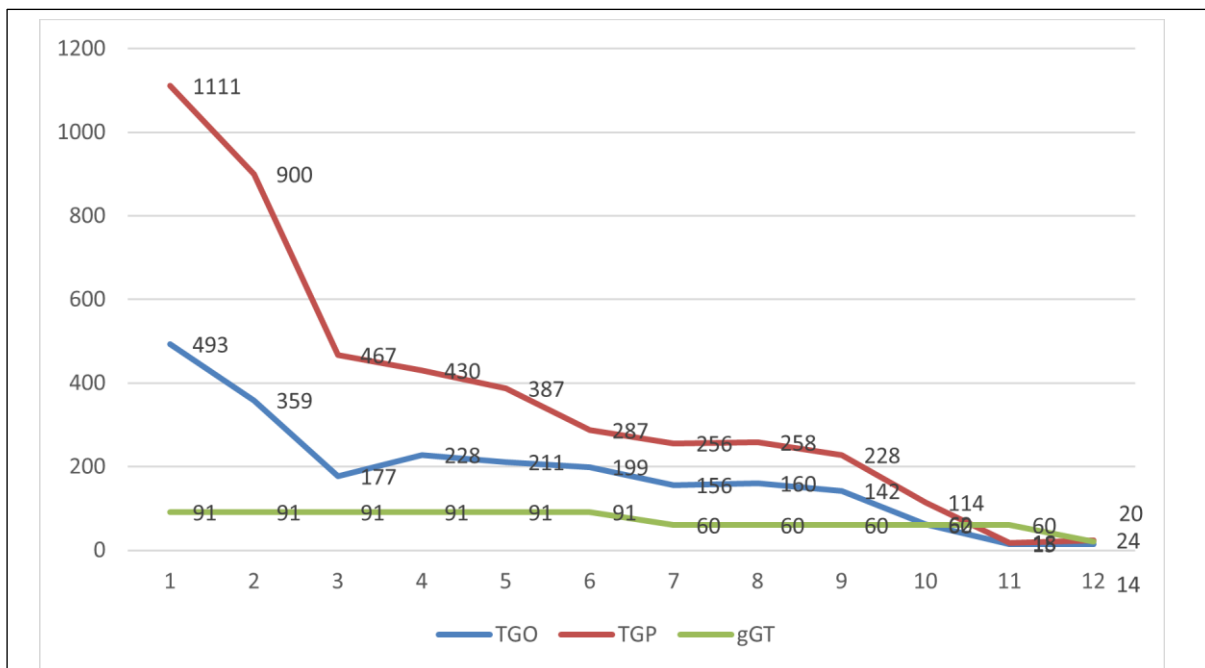


Fig-2: Evolution of patient's transaminase and gGT (Glutamyl Transferase)

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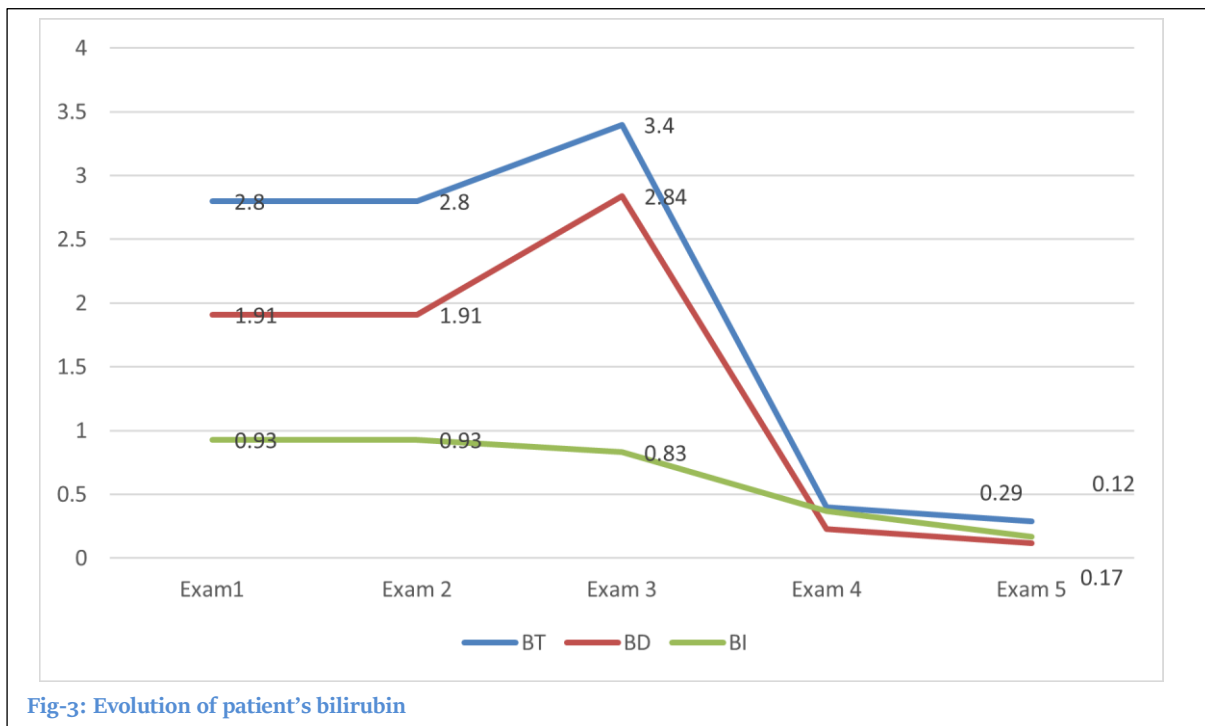


Fig-3: Evolution of patient's bilirubin

The patient continued to take enoxaparin, ASA (100 mg on daily basis), and multivitamin complex during hospitalization, except for vitamin B12, due to high rates of it reported in laboratory exams (2.00pg/mL). She had satisfactory evolution after the application of the support measures was discharged, and remains under follow-up with a hematologist and obstetrician. Pregnancy had satisfactory evolution and contractions started at the 36th/37th weeks of pregnancy. The patient was subjected to the Cesarean section by obstetric recommendation. The newborn was in good condition and stayed in joint accommodation. They were discharged after 48h of hospitalization and are well. She did not present relapse, so far. Subcutaneous progesterone was the chosen contraceptive method; all exams are stable.

Discussion

Hepatitis is a multifactor disease, caused by autoimmunity, toxicity due to medication intake, or by infections caused by bacteria, protozoa, or viruses. However, the viral infection is the most common cause of it. Hepatotropic viruses and those that cause systemic infections, such as yellow fever, Dengue, Zika, CMV, can lead to hepatic conditions diagnosed through serology [10]. The patient was subjected to hepatitis A, B, C, and E examination, but her clinical condition was not related to such viruses. Hepatitis D was not

screened because the patient was immune to the hepatitis B virus; she reported positive for anti-HB. Hepatitis D depends on the hepatitis B virus; it

Virus	Hepatitis A virus
	Hepatitis B virus
	Hepatitis C virus
	Hepatitis D virus
	Hepatitis E virus
	Cytomegalovirus
	Epstein Barr virus
	Others
Autoimmunity	Autoimmune hepatitis
	Primary Biliary Cirrhosis
	Primary Sclerosing Cholangitis
Metabolic Disturbance	Non-alcoholic Fatty Liver Disease
	Hemochromatosis
	Alpha-1-antitrypsin Deficiency
	Wilson's Disease
Toxic Substances	Alcoholic Hepatitis
	Drug-induced Liver Disease

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happens in association with virus B or with virus B carriers [12]. The patient was subjected to examinations to screen other viruses, such as Dengue, Zika, CMV, and HTLV); she was negative for all of them and immune to CMV, as well as to toxoplasmosis and rubella, based on exams conducted during prenatal care - results were also negative for brucellosis. We did not identify the possible agent among the most common infectious causes of hepatitis (Table-3).

Abdominal ultrasound was performed to assess liver steatosis during pregnancy since this condition can have symptoms similar to flu, as observed in the herein assessed patient. However, abdominal ultrasound and dopplerfluxometric analysis of the portal system was regular and discarded the possibility of liver steatosis [13].

The patient was subjected to autoimmune hepatitis examination because this hepatitis type is a chronic necroinflammatory liver disease whose triggering agents are not known. It is probably the result of the interaction between genetic predisposition and external triggering agents (infections, drugs, or toxins). Antinuclear (ANA), smooth muscle (SMA), type 1 anti-liver-kidney microsomal (ALKM-1), and antimitochondrial (AMA) are the anti-bodies often screened in clinical practice; the patient was negative for all of them. Besides, the patients' clinical condition did not meet autoimmunity symptoms, which often evolve slowly (weeks to months) from lethargy and asthenia; laboratory changes and physical examination findings can suggest chronic liver disease or even cirrhosis [6,7]. The patient did not have any other autoimmune diseases, so this hypothesis was discarded.

Intrahepatic cholestasis of pregnancy, which has pruritus as its main symptom, mainly on palms of the hands and on foot soles, was another possibility. This pathology leads to increased concentration of bile acids in the blood, increased liver transaminases (which can reach values higher than 1,000 U/L); however, jaundice affects less than 25% of cases and always appears after pruritus. The main element in the herein reported clinical case was jaundice, rather than

pruritus, which made it possible considering other diagnostic hypotheses [10]. It is also important highlighting that intrahepatic cholestasis of pregnancy regresses two to three weeks after delivery, but did not occur in this case report [14-16]. Transaminases and bilirubin decreased during hospitalization when supportive treatment and vitamin B12 replacement was canceled.

The patient took the following medicines: multivitamin complex, intramuscular injectable vitamin B12, sodium enoxaparin (40mg on a daily basis), folate, and ASA (100mg on a daily basis). The possibility of toxicity caused by medicine taking was assessed because of enoxaparin and ASA; however, doses were only prophylactic. According to the Brazilian Society of Hepatology, ASA is a safe drug for adults and children; it is rarely associated with hepatotoxicity, except for cases of supra-therapeutic doses, which did not happen [11]. Therefore, hepatotoxicity is dose- - levels higher than 25 mg/100 mL - and time-dependent. Resolution was quick after drug withdrawal; it can be reintroduced at low doses, if necessary. Salicylates can lead to hepatotoxicity; therefore, there is no advantage in replacing one aspirin for another. Histopathological findings showed non-specific focal hepatitis with hepatocellular degeneration [11]. However, there was a bilirubin rate decrease and transaminases recovery, even with medication maintenance; this outcome shows that ASA was not the cause of her liver condition. Enoxaparin can cause asymptomatic hepatic enzymes to increase up to three times the reference value [12]. However, the patient kept on taking the medicine during pregnancy because of her clinical condition; there were transaminase and bilirubin reduction. Therefore, the only medication canceled was vitamin B12, due to its high circulation level. Vitamin B12, both in parenteral and oral forms, is not associated with high transaminase activity and with apparent clinically acute liver damage; it is an unlikely etiology of hepatocyte disease [17].

Hepatic lesions can cause liver transaminases (AST and ALP) to increase, malaise, and jaundice, as observed in the assessed patient. Besides, she reported high serum vitamin B12 level assumingly associated

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with liver damage, rather than with the prescribed replacement, since the liver is the main reservoir of this vitamin in the body and accounts for its metabolism [18]. The cause of her hepatitis was nonspecific; it was an unusual infection, since fever was recorded before its clinical manifestation, this outcome can be associated with the likelihood of natural predisposition to develop the disease. The functional deficit of vitamin B12 can have clinical consequences similar to those caused by vitamin deficit because of changes in its transport and delivery to cells [18-21]. The patient is under hematological and hepatological follow-up and showed no relapse, so far.

Conflict of Interest

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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