Hyperbilirubinemia with Unusual Dermatologic Signs: A Diagnostic Puzzle

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ABSTRACT

Jaundice, characterized by yellow discoloration of the skin, mucous membranes, and sclera, results from hyperbilirubinemia and is uncommon in adults. Its occurrence often signals serious underlying conditions. Hyperbilirubinemia may also present with cutaneous manifestations, including xerosis, hyperpigmented plaques, and erythematous rashes. A 47-year-old woman presented with hyperbilirubinemia, transaminitis, and cutaneous manifestations, including hyperpigmented plaques on the face, erythematous rashes on the hands and feet, and yellowish discoloration of the skin. Despite extensive evaluation, including viral hepatitis screening, autoimmune markers, and imaging, a definitive diagnosis remained elusive. The clinical features and laboratory findings suggested Primary Biliary Cholangitis (PBC) as the most likely diagnosis, although further confirmation through advanced serological testing and liver biopsy was needed. Treatment with ursodeoxycholic acid (UDCA) and high-dose oral methylprednisolone showed clinical improvement but persisted in transaminitis with a normal ultrasonographic appearance. This case emphasizes the importance of recognizing cutaneous signs in systemic diseases and the need for a comprehensive diagnostic approach in resource-limited settings.

Keywords*: cutaneous manifestations; hyperbilirubinemia; Primary Biliary Cholangitis (PBC); transaminitis*

INTRODUCTION

Yellowish discoloration of the skin, mucous membranes, and the sclera of the eyes is caused by excessive bilirubin accumulation in the body. This condition, known as jaundice, occurs due to hyperbilirubinemia.[1] Although jaundice is relatively rare in adults, its occurrence typically shows a serious underlying pathology. Diagnosing jaundice requires more than physical examination, as the causes are highly diverse, ranging from pre-hepatic, intrahepatic, to post-hepatic disorders.[1] Hyperbilirubinemia, in addition to causing jaundice, may also lead to cutaneous manifestations, such as ichthyosis/xerosis, pallor, excoriation, hyperpigmentation of palmar creases, clubbing, and slight edema. The manifestations are often associated with primary hepatobiliary disorders.[2] This case report discusses a 47-year-old woman admitted with transaminitis and hyperbilirubinemia

accompanied by erythematous maculopapular rashes, scaling desquamation on the hands and feet, and itching. The most prominent skin manifestation was the appearance of hyperpigmented plaques on the face. The patient was treated at a hospital in Malang, East Java, Indonesia. Despite hospitalization, a definitive diagnosis could not be established due to limitations in available medical services and cultural barriers, which hindered the patient's willingness to undergo certain medical procedures. This case offers a valuable opportunity to explore the likely diagnosis from a medical perspective, emphasizing the challenges posed by such constraints.

CASE ILLUSTRATION

A 47-year-old woman was admitted with elevated SGOT, SGPT, and bilirubin levels, accompanied by the presence of hyperpigmented plaques covering her entire face for the past week. (**Figure 1-A**). The skin lesions initially presented as erythematous rashes on the hands and feet, accompanied by itching over the past two months (**Figure 2-A**). The patient also reported yellow discoloration of the body and eyes, along with dark brown urine resembling tea, during the same period. According to the medical history, multiple surgeries have been performed, including appendectomy due to appendicitis (2010), cesarean section (2011), hysterectomy (2013), mastectomy of the right breast due to multiple fibroadenomas (2023), and mastectomy of the left breast due to multiple fibrocystic changes (2024). The patient had no history of allergies and denied alcohol consumption. During the physical examination, the patient's vital signs were within normal limits, and hyperpigmented crusts were observed across her face (Figure 1-A) along with erythematous rashes, xerosis, desquamation, and yellowish discoloration on the hands and feet (Figure 2-B). Cardiovascular, pulmonary, and Laboratory examination (**Table 1**) revealed leukocytosis (15,230/mcL), eosinophils at 1.8%, neutrophils at 81.5%, and lymphocytes at 5.6%. Blood chemistry analysis showed hyperbilirubinemia (31.20 mg/dL) of parenchymal origin, accompanied by elevated AST (401.4 U/L) and ALT (310.2 U/L). A prior examination conducted at another hospital a month earlier also showed a total increase in bilirubin (18.8 mg/dL), AST (637.0 U/L), and ALT (537.0 U/L). Abdominal ultrasonography did not reveal any pathological abnormalities (**Figure 3**). Screening for viral hepatitis markers (A, B, and C) yielded negative results, and coagulation profiles, including APTT and PT, were within normal limits. The kidney function tests were also within normal limits. The ANA

Table 1. The patient's laboratory examination results on admission (12/11/2024)

Laboratory test	ER Admission	Reference Value
Hemoglobin	13.9	12 – 16 g/dL
Leukocyte (WBC)	15.23	4.3 – 10.8 10^3/mcL
Eosinophil	1.8 % (270/mcL)	1 – 3 %
Neutrophil	81.5% (12.41/mcL)	42.5 – 71%
Lymphocyte	5.6% (850/mcL)	20.4 – 44.6%
Thrombocyte	299	150 – 400 10^3/mcL
Random Blood Glucose	103	< 140 mg/dL
SGOT (AST)	401.4	< 35 U/L
SGPT (ALT)	310.2	< 41 U/L
Total Bilirubin	31.20	0.3 – 1.0 mg/dL
Direct bilirubin	18.66	< 0.2 mg/dL
Indirect Bilirubin	12.54	< 0.1 mg/dL
Ureum	17.6	17 – 36 mg/dL
BUN	8.25	7 – 23 mg/dL
Creatinine	0.62	0.6 – 1.1 mg/dL

WBC, White Blood Cell; SGOT, Serum Glutamic-Oxaloacetic Transaminase; AST, Aspartate Aminotransferase ; SGPT, Serum Glutamic-Pyruvic Transaminase; ALT, Alanine Aminotransferase; BUN, Blood Urea Nitrogen

Table 2. The aminotransferase and bilirubin levels on monitoring

Laboratory test	(12/11/2024)	(12/14/2024)	12/18/2024	Reference Value
SGOT (AST)	401.4	217.8	265.4	< 35 U/L
SGPT (ALT)	310.2	219.7	156.3	< 41 U/L
Total Bilirubin	31.20	29.17	30.76	0.3 – 1.0 mg/dL
Direct bilirubin	18.66	18.20	19.40	< 0.2 mg/dL
Indirect Bilirubin	12.54	10.97	11.36	< 0.1 mg/dL

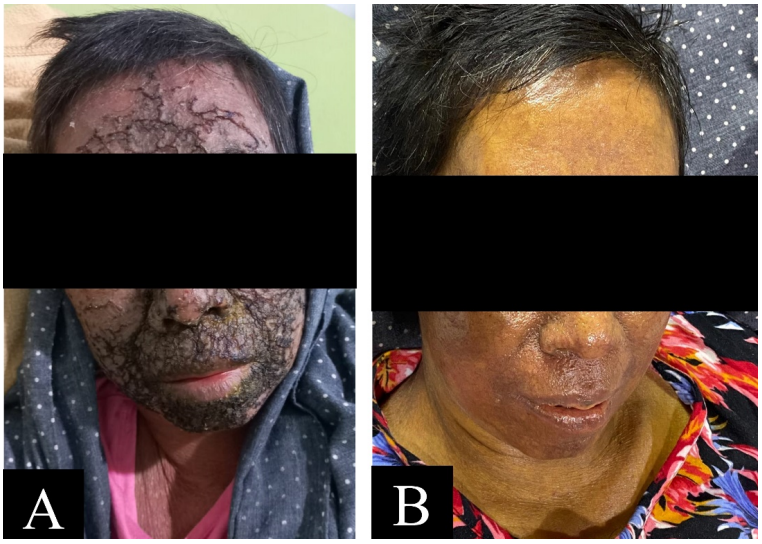

Figure 1. Hyperpigmentation crust on the face (**A**); Resolving hyperpigmentation crust after medication (**B**)

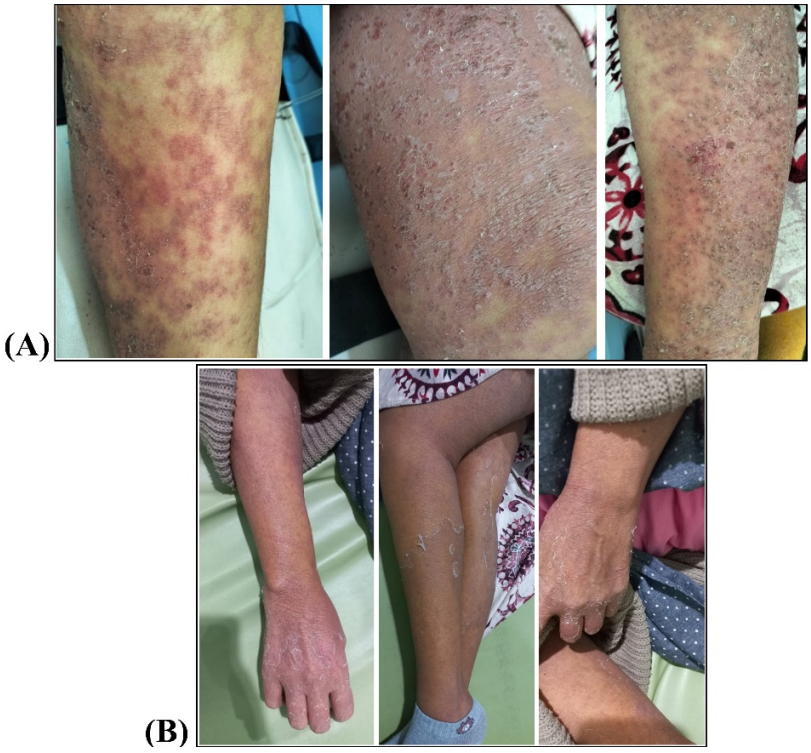

Figure 2. Maculopapular erythematous rash with desquamated skin on the hand and foot (**A**); Xerosis erythematous rash, desquamated skin on the hand and foot during hospitalization (**B**)

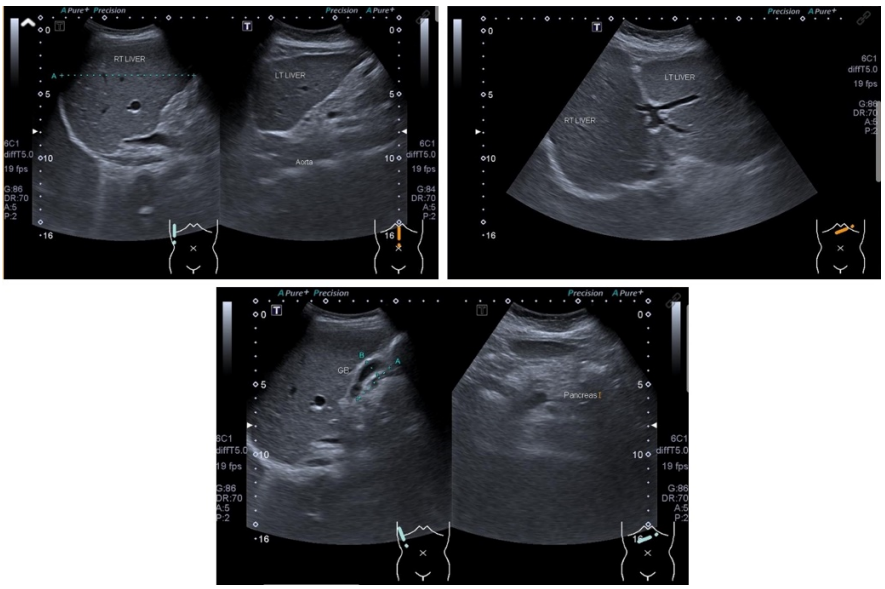

Figure 3. Normal ultrasonographic appearance

test (10.00 AU/mL) was negative, and AFP levels were recorded at 11.90 IU/mL. During hospitalization, the patient was treated with glycyrrhizine infusion drip in normal saline daily, high-dose methylprednisolone orally (32 mg–16 mg–0) followed by a tapering off regimen, saline compresses (0.9% NaCl), and 10% urea cream to address facial skin lesions. Clinically, the patient showed improvement, with fading hyperpigmented crusts on the face (**Figure 1-B**). However, bilirubin, AST, and ALT levels remained persistently elevated without significant reductions (**Table 2**).

Based on the clinical data, laboratory findings, and supporting examinations above, a definitive diagnosis remains unclear. The patient's primary problem includes elevated transaminase and bilirubin levels of unknown origin, accompanied by abnormal skin manifestations (xerosis, desquamation, yellow skin, erythema, skin eruption), and probable related hyperbilirubinemia. Identifying the most possible definitive diagnosis for this patient is a critical focus for further discussion.

DISCUSSION

Based on the patient's history and clinical examination, the findings included yellowish discoloration of the skin, maculopapular erythematous rashes on the hands and feet, hyperpigmented crusts on the face, hyperbilirubinemia, and transaminitis. Hepatitis virus infections were excluded due to the absence of clinical symptoms and negative viral markers (Hepatitis A, B, and C). According to the ANA test, AFP, and abdominal ultrasound results, diagnoses involving autoimmune liver diseases, malignancies, or bile duct obstructions were also excluded. Since there was no history of drug or alcohol consumption, liver damage caused by substances could also be ruled out. Considering the available data, a 47-year-old woman with persistent elevation of alkaline phosphatase and hyperbilirubinemia without obstruction or bile duct dilation, and no history of drug, herbal, or alcohol intake, the most likely diagnosis is Primary biliary cholangitis.[3]

primary biliary cholangitis is a chronic autoimmune disorder that impacts the intrahepatic bile ducts, resulting in cholestasis and fibrosis.[4] The disease predominantly affects women, especially occurring in about 1 in 1000 women over the age of 40, with factors such as genetic predisposition, hormonal influences, and epigenetic changes playing a role.[5-7] This case aligns with the classical presentation of PBC, given the persistent hyperbilirubinemia, transaminitis, and absence of obstructive biliary pathology. Further serological testing and liver biopsy are crucial for confirmation.

Hormonal fluctuations, particularly elevated estrogen levels, are a risk factor in patients with fibrocystic breast disease. Elevated estrogen increases DNA synthesis, mitotic activity, cell proliferation, and differentiation, potentially predisposing individuals to benign atypical breast tumors. A case-control study conducted by Milena Brkic et al. involving 50 patients with fibrocystic breast disease showed a higher estrogen-to-progesterone ratio (E2/P) compared to 40 control patients.[8] Estrogen is also known to increase IFN-γ production, triggering anti-mitochondrial antibodies (AMA) in circulation, leading to bile duct damage associated with PBC.[7] Therefore, fluctuations in estrogen hormone levels are considered a contributing factor to the development of PBC and fibrocystic breast disease in this patient.

The most commonly reported symptoms in PBC patients include fatigue (20%-85%), followed by pruritus (20%-75%), jaundice (10%-60%), xanthomas (15%-50%), dyslipidemia (>75%), and osteoporosis (35%).[9] Occasionally, symptoms may mimic other conditions such as Sjögren's syndrome, thyroid disorders, and systemic sclerosis, necessitating vigilance during diagnosis. The screening tests, including Anti-Ro/SSA, Anti-La/SSB, thyroid panels, and anticentromere antibodies, are essential for excluding these conditions.[10] In addition, PBC patients may experience dermatological symptoms such as lichen planus, vitiligo, and psoriasis.[11] A prospective study conducted by Koulentaki et al. involving 49 PBC patients found that pruritus, xerosis, dermographism, and melanosis were more frequently observed. Moreover, 38.7% of patients experienced dermatological lesions as their initial presenting symptoms. These findings emphasize the importance of recognizing cutaneous manifestations as early indicators for the detection of PBC.[12]

To establish a diagnosis of PBC and exclude differential diagnoses, further investigations such as Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI), Magnetic Resonance Cholangiopancreatography (MRCP), autoantibody markers, and liver biopsy are required. CT and MRI play an important role in determining the diagnosis and ruling out other possible causes of abnormalities. Additionally, these modalities can assess disease staging and predict prognosis in PBC cases. CT and MRI allow for the evaluation of various abnormalities, including liver morphology changes, parenchymal structure alterations, irregular bile duct configurations, lymphadenopathy, portal hypertension, and cirrhotic complications. MRI with gadoxetic acid contrast offers deeper insights into liver function assessment in PBC patients.[13] MRCP often appears normal in the early stages of PBC. However, in advanced stages, it may reveal segmental dilation of intrahepatic bile ducts, poor visualization of ducts, or strictures. MRCP can also differentiate PBC from other conditions, such as Primary Sclerosing Cholangitis (PSC). This is characterized by beaded ducts and a "pruned-tree" appearance of bile ducts, or IgG4-related sclerosing cholangitis, which typically shows duct strictures accompanied by proximal dilation.[13]

To establish a definitive diagnosis, serological testing for anti-mitochondrial antibodies (AMA) and liver biopsy should be considered. So, the autoantibody tests and liver biopsy are the next recommended steps for this case. Serological testing for AMA is the primary specific marker for diagnosing PBC. It is considered positive if the titer exceeds 1:40 on Indirect Immunofluorescence (IIF) or ≥ 25 units on Enzyme-Linked Immunosorbent Assay (ELISA). In cases where AMA results are negative, additional markers such as anti-nuclear antibodies (anti-gp210 or sp100), which have over 95% specificity, can be tested.[3,4] If these markers are also negative, a liver biopsy should be performed. Histopathological findings in PBC typically reveal non-suppurative destructive cholangitis, characterized by epithelioid granulomas situated near damaged bile ducts, commonly referred to as florid duct lesions. In addition to confirming the diagnosis in cases with negative serology, a liver biopsy is also valuable for ruling out differential diagnoses such as autoimmune hepatitis (AIH) or non-alcoholic steatohepatitis (NASH). It is further useful for risk stratification following a confirmed

diagnosis of PBC.[3,4]

The improvement in liver function associated with UDCA is attributed to its mechanisms of action, which include stimulating hepatobiliary secretion, inducing bile acids that suppress hepatocyte apoptosis, protecting cholangiocytes from damage caused by toxic bile acids, and enhancing Cl^-/HCO_3^- secretion via Ca^{2+}-dependent pathways in cholangiocytes. These mechanisms play an important role in supporting liver function and improving the patient's clinical condition.[15] Clinical and laboratory improvements observed in patients receiving UDCA therapy may also help differentiate PBC from PSC. This distinction is important because the use of UDCA in PSC remains controversial and is generally not recommended, as it has not been proven to provide a survival benefit.[16] The patient responded to UDCA therapy with some improvement in bilirubin and transaminase levels. Long-term monitoring is necessary to assess the adequacy of treatment response while waiting for a diagnosis to be confirmed.

CONCLUSION

This case poses a significant diagnostic challenge, as the patient exhibited cutaneous manifestations alongside laboratory findings of hyperbilirubinemia and transaminitis, despite ultrasound imaging revealing no abnormalities. Therefore, further investigations are necessary, including serological tests, advanced imaging techniques, and liver biopsy. One of the potential diagnoses to be considered is PBC. Considering the rarity of this case and its overlapping features with other conditions, clinicians must enhance their diagnostic approach. This will ensure prompt and accurate treatment while avoiding unnecessary diagnostic procedures.

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CONFLICT OF INTERESTS

The authors declare there is no conflict of interest.

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