

## A challenging case of jaundice and febrile uncommon rash in an immunocompetent male patient

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### QUESTION

A 39-year-old man presented to the Infectious Diseases Clinic in July 2017 with jaundice and febrile uncommon rash.

His medical history showed hypercholesterolemia without medical treatment and anxious depressive syndrome treated with sertraline. He had no known allergies or no significant cardiovascular risk factors except for smoking. His current illness started 11 days earlier with high fever, chills, and malaise. His symptoms persisted despite oral treatment with acetaminophen 1500 mg/day for 4 days, ibuprofen 800 mg/day for 4 days, and amoxicillin 2000 mg/day for 2 days. Thereafter, he developed edematous maculopapular erythematous skin rash on the palms and soles, scleral jaundice, nausea, and physical fatigue. He was admitted in another infectious diseases unit where he received treatment with ceftriaxone 2 g/day for 2 days, followed by oral doxycycline 200 mg/day and intravenous (iv) levofloxacin 750 mg/day for 4 days. After 7 days of unfavorable evolution, the patient was discharged on request.

At presentation in our clinic, he was overweight with a body mass index of 28.4 kg/m<sup>2</sup> and had an impaired general condition, jaundice, symmetrical maculopapular erythematous skin rash on the palms and soles, epithelial desquamation of the hand and feet, and painless hepatomegaly at 3 cm below the costal margin (Figure 1). He had no fever, respiratory or cardiovascular abnormality, and meningeal syndrome. His laboratory tests showed leukocytosis (12,170/μL), neutrophilia (81.1%), low prothrombin concentration (59%), and inflammatory syndrome (C-re-

active protein 93.2 mg/L, fibrinogen 1034 mg/dL, ferritin 3403 ng/mL, and erythrocyte sedimentation rate 78 mm/h). Blood chemistry revealed mixed hyperbilirubinemia (10 mg/dL), with the predominance of the conjugated fraction (8.6 mg/dL), increased γ-glutamyl transpeptidase and alkaline phosphatase levels (1198 U/L and 501 U/L, respectively), and moderate hepatic cytolysis (alanine aminotransferase 169 U/L and aspartate aminotransferase 120 U/L). His chest X-ray and abdominal ultrasound revealed no pathological changes except for homogeneous hepatomegaly. In addition to nasal, pharyngeal, and rectal swabs to assess the carriage of multidrug-resistant bacteria, urine and blood cultures were collected, all of which yielded negative results. Empirical antibiotic treatment with a combination of iv meropenem 3 g/day and oral doxycycline 200 mg/day was started. After 5 days, the patient developed dry cough and fever. The anti-infective regimen by a combination of iv meropenem, linezolid, levofloxacin, and anidulafungin in common dosages was increased. We have associated steroids (dexamethasone 8 mg/day) owing to the suspicion of autoimmune disease. Contrast-enhanced magnetic resonance cholangiography revealed homogeneous hepatomegaly without dilatation of the bile ducts. Thereafter, he developed respiratory dysfunction with dyspnea and hypoxemia (peripheral O<sub>2</sub> saturation 90%) along with the generalization of skin rash and the appearance of white spot lesions on the oral mucosa (Figure 2). Contrast-enhanced computer tomography of the thorax, abdomen, and pelvis showed bronchiolitis and multiple axillary, mediastinal, and abdominal subcentimeter lymphadenopathies.

**What is the patient's most likely diagnosis?**

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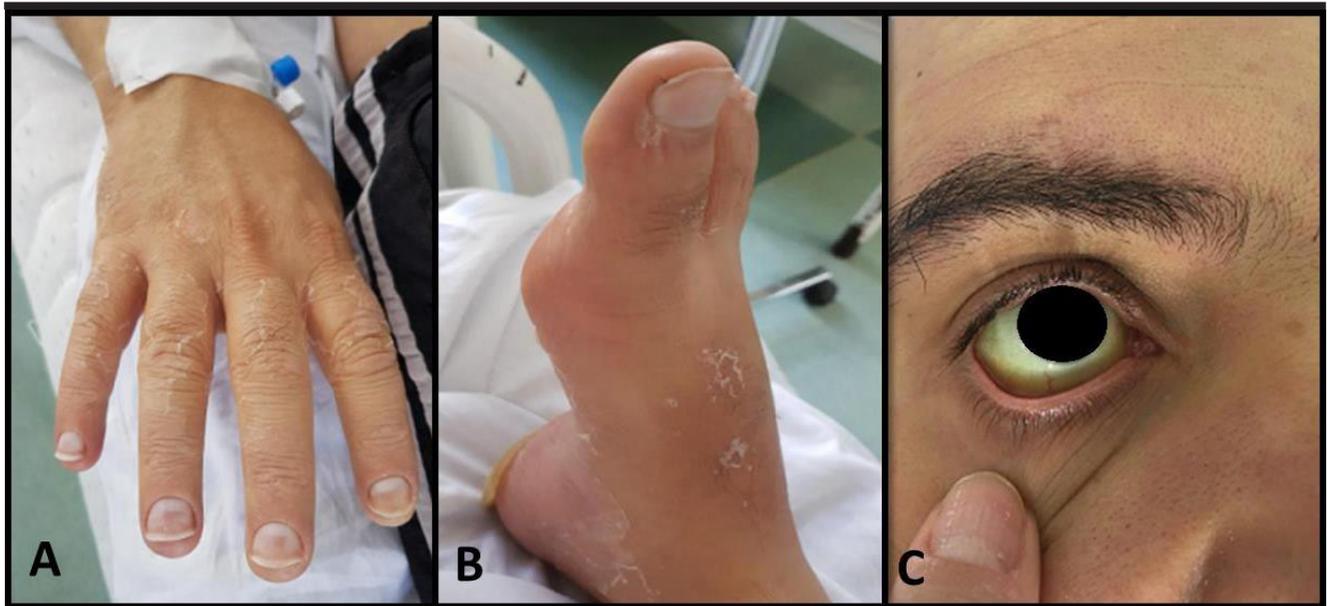


Figure 1. a-c. Status post erythema and edema of the hand with subsequent epithelial desquamation (a); status post erythema and edema of the feet with subsequent epithelial desquamation (b); clinical aspect of the scleral and cutaneous jaundice (c)

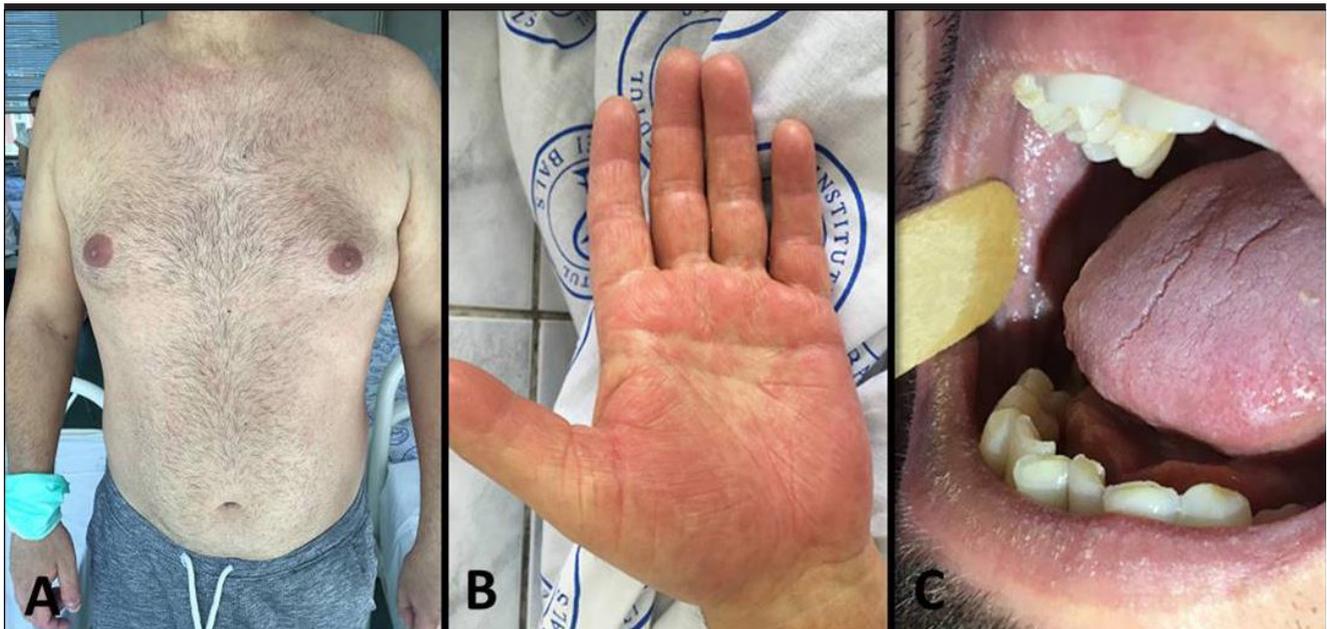
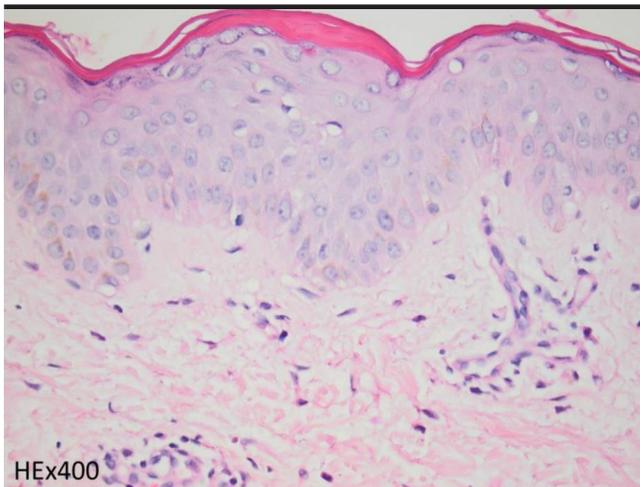


Figure 2. a-c. Generalized maculopapular erythematous rash (a); maculopapular erythematous rash of the palms (b); white spots lesions covering the oral mucosa (c)

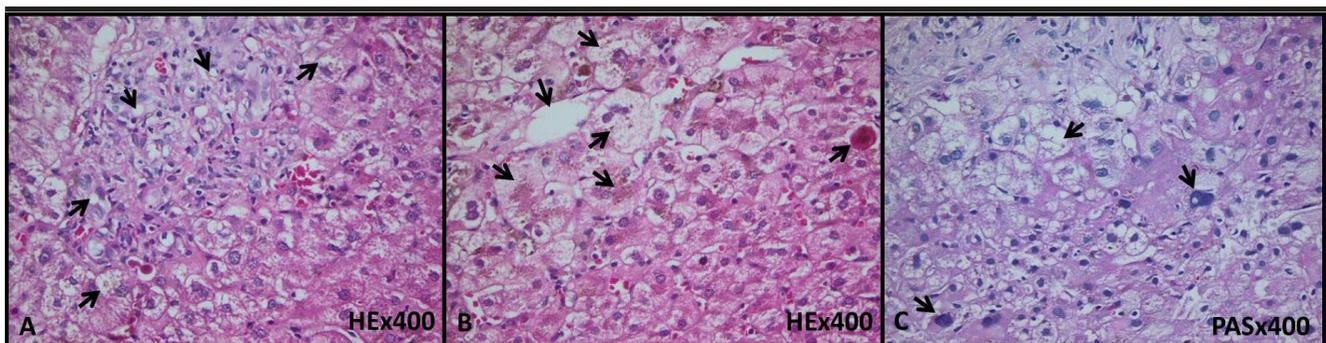
**ANSWER**

Based on existing information, the patient had flu-like syndrome, jaundice, exfoliative skin rash, and severe cholestatic hepatitis. We eliminated a wide range of differential diagnoses, such as acute viral diseases (Epstein-Barr virus, cytomegalovirus, enterovirus, parvovirus B19, human T lymphoma virus, and hepatitis A, B, C, or E), acute bacterial diseases (sepsis, leptospirosis, cholangitis, staphylococcal and streptococcal scalded skin syndromes, Q fever, syphilis, *Mycoplasma pneumoniae*, and *Brucella* species), autoimmune conditions, malignancies, and obstructive icterus. Subsequent blood tests showed severe lymphopenia with a very low level of CD4



**Figure 3.** Minimal hyperkeratosis with parakeratosis (keratinocyte nuclei preserved in the corneum stratum), minimal acanthosis, discrete perivascular lymphomonocytic inflammatory reaction in the superficial dermis

T cell (38/ $\mu$ L) and CD8 T cell counts (109/ $\mu$ L) with a CD4/CD8 ratio of 0.34. The fourth generation of human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay test was negative, and serum HIV RNA was undetectable, excluding acute HIV infection. Unexpectedly, the serology (IgM) for measles was positive, being initially interpreted as a possible false-positive reaction. After resuming anamnesis, measles vaccination was identified in 1979 without additional information about the vaccine. The patient also reported the existence of an airborne contact with an undiagnosed eruptive disease in a child approximately 10 days before the onset of his current disease. In the context of severe cellular immunosuppression with unfavorable clinical outcome under broad-spectrum anti-infective treatment, we switched the treatment to cover the main opportunistic infections (*Pneumocystis jiroveci*, disseminated *Mycobacterium tuberculosis*, or *Mycobacterium avium* complex). The patient had a good evolution after switching therapy with a combination of oral cotrimoxazole, clarithromycin, ethambutol, and iv amikacin plus moxifloxacin for 7 days. In order to have a definite diagnosis and to avoid unnecessary treatment with potential side effects, we decided to perform skin and liver biopsies. After 3 days, the patient developed visual disturbances with blurred vision. On ophthalmological examination, the clinical pattern of measles keratitis was noted. Skin biopsy showed histological features suggestive of viral exanthema (Figure 3). Liver biopsy revealed portal ductal reaction, focal interface hepatitis, periportal hepatocyte apoptosis with the presence of apoptotic eosinophilic bodies (Mallory bodies), centrilobular cholestasis, rare multinucleate giant hepatocytes, rare hyperchromic, pleomorphic nuclei, and hepatocyte ballooning degeneration (Figure 4). The



**Figure 4. a-c.** Portal ductal reaction (increased number of portal bile ducts and inflammatory infiltrates with periductal and intraepithelial lymphocytes, monocytes and neutrophils), focal interface hepatitis, periportal cholestasis with the presence of green-brown bile pigment granules inside the ballooning hepatocytes (a); centrilobular cholestasis (intrahepatocytic and intracanalicular green-brown bile pigment granules, predominantly around the centrilobular vein), apoptotic eosinophilic bodies (Mallory bodies), multinucleate giant hepatocyte and hepatocyte ballooning degeneration (b); rare hyperchromic, pleomorphic (c)

histological pattern is consistent with a viral cytopathic effect without being able to exclude nonspecific hepatocyte regenerative or degenerative changes. Atypical measles syndrome (AMS) with severe cholestatic hepatitis was diagnosed as the final finding. We have discontinued anti-infective and steroid treatments with progressive improvement of clinical and biological abnormalities under treatment with ursodeoxycholic acid 15 mg/kg/day. The patient was discharged on day 26 of admission. At follow-up visits, he was in good clinical condition, and blood test results were normal.

Atypical measles syndrome is a rare variant of measles as defined by an older age distribution, high and prolonged fever, polymorphic skin rash usually starting on the hands and feet, pulmonary infiltrates, and hepatobiliary impairment. The emergence of AMS has been linked to a prior immunization with the original killed measles vaccine (1). Romania is experiencing a large outbreak of measles since February 2016 mainly due to the failure to maintain the high coverage of childhood immunization. Only few cases of AMS have been published in the literature. Liver dysfunction in measles was first described in 1960 by Berry who reported a 29-year-old woman with measles and increased liver enzymes (2). The first case of measles with acute hepatitis and clinical jaundice has been reported in 1982 (3). Two distinct patterns of measles-associated liver impairment have been identified. The first type was defined by moderate elevation of transaminases. It was often asymptomatic and appeared in the early phase of the disease with resolution within days. The second pattern was characterized by jaundice and cholestasis. Generally, it was symptomatic and occurred in the early convalescence phase and persisted for  $\geq 2$  weeks. Various pathogenic mechanisms for measles-associated hepatitis have been proposed. One mechanism is a direct viral cytopathic effect which could explain the early type of measles hepatitis. The other mechanism is a host-mediated immune response to measles virus infection, possi-

bly explaining the occurrence of cholestatic hepatitis in the convalescent phase of the disease (4). Therefore, the clinical, biological, and histopathological characteristics highlighted in our case support the hypothesis that measles-associated hepatitis has been linked to the involvement of both pathogenic mechanisms.

We presented a challenging diagnosis of AMS in an adult patient with severe cholestatic hepatitis, requiring a large number of investigations to exclude multiple differential diagnoses. In the context of an ongoing measles epidemic, our main message is aimed to increase the physician awareness about AMS in order to reduce the delay of diagnosis and to avoid invasive procedures and unnecessary treatment.

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