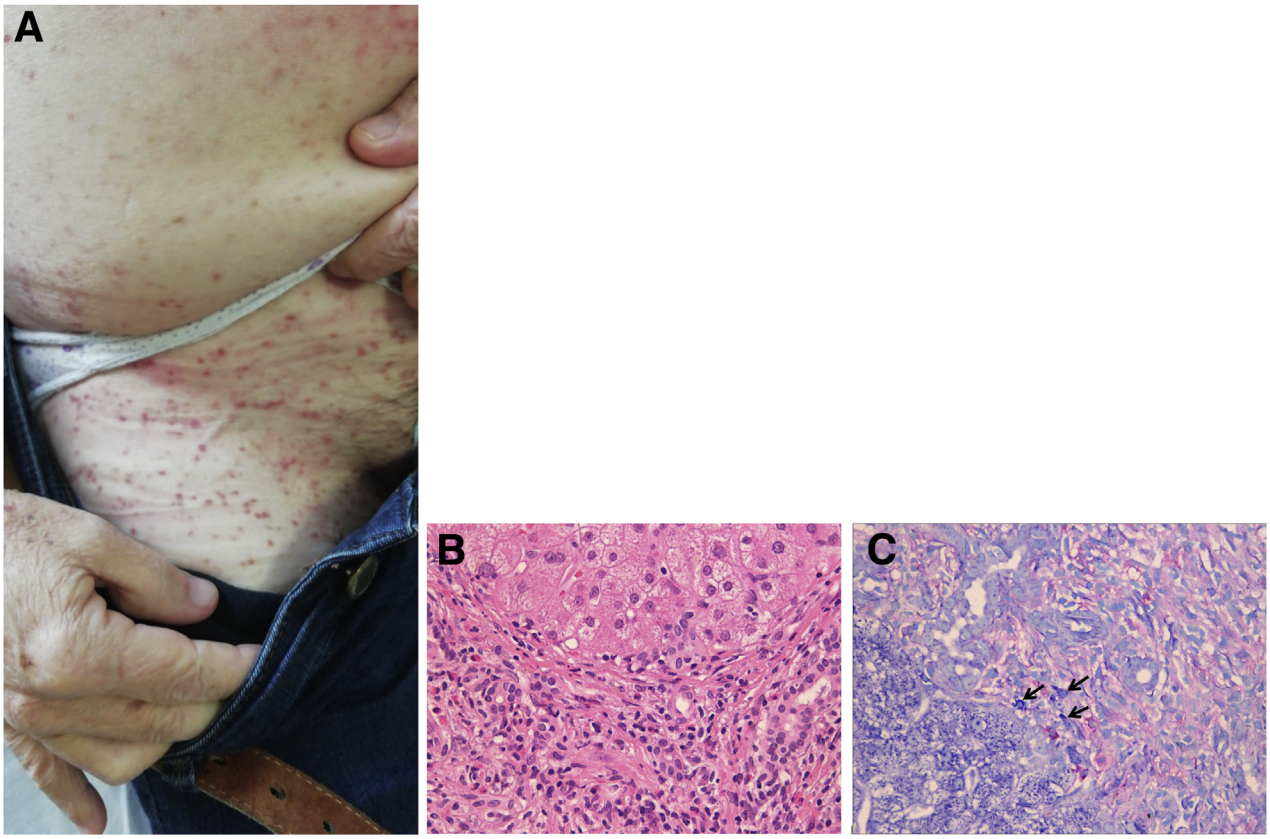
A Case of Unexplained Cutaneous Lesions, Cholestatic Hepatitis, and Noncirrhotic Portal Hypertension in a Female Patient

Joana Carvão, Vítor Magno Pereira, and Luís Jasmins

Gastroenterology Department, Hospital Central do Funchal, Funchal, Portugal



Question: A 57-year old woman with a previous history of contrast-related anaphylaxis was referred to the gastroenterology department with worsening liver function tests. She developed recurrent abdominal pain, diarrhea, significant weight loss, pruriginous generalized skin rash, and increased abdominal volume over 1 year.

Physical examination revealed generalized small reddish monomorphic macules on the trunk and thighs (Figure *A*), hepatosplenomegaly, peripheral lymphadenopathy, and ascites. Blood tests showed normocytic normochromic anemia (hemoglobin 9.4 g/dL), monocytosis ($1.3 \times 10^3/\mu L$), thrombocytopenia ($97 \times 10^3/\mu L$), slight international normalized ratio prolongation, and a marked elevation of cholestasis parameters without jaundice (aspartate aminotransferase, 60 U/L; alanine aminotransferase, 56 U/L; gamma-glutamyl transferase, 324 U/L; and alkaline phosphatase, 1277 U/L).

Abdominal Doppler ultrasound examination and a computed tomography scan revealed homogeneous hepatosplenomegaly (without signs of chronic liver disease), signs of portal hypertension without thrombosis of the splenoportal axis, moderate ascites, and intra-abdominal, axillary, and inguinal lymphadenopathies. Upper endoscopy showed esophageal varices and portal hypertensive gastropathy.

Laboratory studies for chronic hepatopathy, infectious agents, and angiotensin-converting enzyme were negative. Bone marrow biopsy revealed granulomatous myelitis, and both lymphadenopathy and skin biopsies showed increased mononuclear cells.

Because the previous workup did not provide a diagnosis, a percutaneous liver biopsy was performed, and revealed moderate expansion of portal structures, with irregular contour (Figure *B*) and infiltration with numerous mastocytes, occasionally in an atypical form (*arrow* in Giemsa stain in Figure *C*), and focal necrosis with no evidence of fibrosis. These findings were confirmed in immunostaining, revealing C-KIT positivity. Serum trypsin levels were >20 ng/L. A second look revision of skin and bone marrow biopsies was obtained, revealing occasional scattered mastocytes (C-KIT+).

What is the most likely diagnosis in this patient?

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Correspondence:
Address correspondence to: Joana Isabel Jardim Carvão, Gastroenterology Department , Hospital Central do Funchal, Avenida Luís de Camões n° 57, 9004-514 Funchal, Portugal. e-mail: joanacarvao@hotmail.com.

Conflicts of interest
The authors disclose no conflicts.

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Answer to: Image 6: Aggressive Systemic Mastocytosis

Together these findings were consistent with the diagnosis of aggressive systemic mastocytosis (SM). SM is characterized by organ infiltration of abnormal mast cells with or without cutaneous involvement.[1] Further genetic testing revealed D816V mutation in the c-Kit gene.

Clinical manifestations are related to the infiltration of monoclonal mast cells in several organs (eg, hepatosplenomegaly, lymphadenopathies) and to the release of mast cell mediators (eg, urticaria, diarrhea, abdominal cramping).[1] Cutaneous involvement in adult-onset SM typically consists of small monomorphic maculopapular lesions, predominantly on the trunk and thighs, such as our patient.[2] Gastrointestinal and liver involvement are seen in $\leq$80% of the patients with SM and have a broad spectrum of manifestations.[3] Liver function tests are frequently abnormal with a typical elevation of alkaline phosphatase. The latter correlates with liver size, amount of liver fibrosis and mast cell infiltrate.[3] Characteristic biopsy findings include, inflammatory cellular infiltrates (100%), anisocytosis (100%), increased fibrosis (14%–100%), hepatocyte changes, including focal necrosis (59%), extramedullary hematopoiesis (54%), cirrhosis ($\leq$15%), portal venopathy or veno-occlusive disease (12%), and cholestasis (8%). Inflammatory infiltrates reveal an increased number of mast cells, mostly distributed in the portal area.[3] Noncirrhotic portal hypertension and ascites occur owing to the blocking of sinusoidal and venous flow by massive mastocyte infiltration and implicate a poorer prognosis.

The diagnosis of SM may be delayed for several months or years owing to a complex clinical scenario. This case was particularly challenging because biopsies did not initially provide the diagnosis. In fact, the first suspicion was of lymphoproliferative disease or sarcoidosis. Therefore, a high level of clinical suspicion up front for SM and a multidisciplinary team approach are essential for the diagnosis.

Cytoreductive therapy is frequently required in aggressive SM to ameliorate disease-related organ dysfunction. Pharmacologic agents directed at MC degranulation (eg, H1/H2-antagonists) should also be considered for symptom alleviation.[1] The patient was started on cladribine, and laboratory workup at 6-month revealed significant improvement, with normalization of blood count, coagulation parameters, and liver function tests (Table 1).

Table 1. Blood Tests from Admission and 6 Months after Therapy

	Admission	6 Months after Therapy
Leucocytes ($\times 10^3/\mu$L)	11	3.3
Monocytes ($\times 10^3/\mu$L)	1,3	0.8
Hemoglobin (g/dL)	9,4	11,3
Platelets ($\times 10^3/\mu$L)	97	176
International normalized ratio	1,35	-
Prothrombin time (sec)	15,2	-
Aspartate aminotransferase/alanine aminotransferase (U/L)	60/56	24/12
Gamma-glutamyl transferase/alkaline phosphatase (U/L)	324/1277	156/503
Albumin (g/L)	33,6	35,9

Clinicians should consider infiltrative disease, particularly SM, as a differential diagnosis in cases of portal hypertension of unknown etiology, especially in a patient with a history of anaphylaxis and monomorphic maculopapular skin lesions.

Keywords: Non-cirrhotic Portal Hypertension; Mastocytosis; Maculopapular Cutaneous Mastocytosis.

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