How skin and liver can lead to diagnosis

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A 73-year-old woman was referred by her hematologist for cholestasis of unknown origin. She was recently diagnosed with chronic myelomonocytic leukemia grade 0 in a context of fatigue, night sweats, weight loss and monocytosis. A PET-CT showed hepatosplenomegaly and multiple centimetric adenopathy. The diagnosis was confirmed by a bone marrow aspiration and biopsy.

Interestingly, the evolution of the patient is marked by the appearance of cholestasis and an erythematous firm skin nodule of the right forearm. The skin lesion was biopsied to rule out a cutaneous localization of the patient's known hemopathy. Histology showed an infiltration of the dermis with a population of immature cells. The immunohistochemical analysis of those cells showed positive CD117 (Fig. 1A) and CD4 staining leading to the diagnosis of a skin localization of the chronic myelomonocytic leukemia.

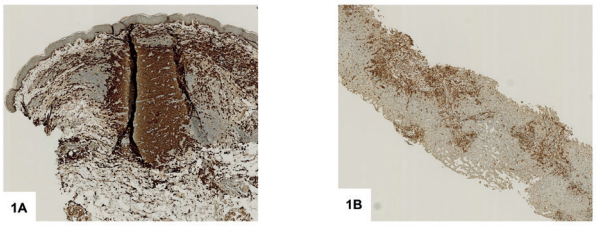

Figure 1. — Skin nodule biopsy revealing a massive infiltration of the dermis with CD117 positive cells (A) and liver biopsy showing an impressive presence of CD25 positive cells within the portal tract and extending in the liver lobule (B).

Table 1. — **Main hematological, systemic and autoimmune diseases affecting the skin and the liver**

Disease	Skin manifestation	Liver finding
Hemopathies		
• Lymphoma	Pruritus, erythematous patches, plaques and nodules	Nodules, mass
• Langherans cell histiocytosis	Brown to purplish papulonodular eruption	Diffuse liver infiltration, nodules, sclerotizing cholangitis
• Malignant histiocytosis	Ulcerated lesions, erythematous plaques	Peliosis hepatis
• Systemic mastocytosis	Maculopapular eruption, mastocytoma, pruritus	Portal hypertension, cholestasis
Systemic diseases		
• Sarcoidosis	Papular lesions, nodular lesions, plaque-like lesions, lupus pernio, erythema nodosum, subcutaneous nodules	Cholestasis, cirrhosis, hepatic vein thrombosis, portal hypertension
• Crohn's disease, Ulcerative colitis	Erythema nodosum, pyoderma gangrenosum, Sweet syndrome	Primary sclerosing cholangitis
• Vasculitis		
○ Periarteritis nodosa	Erythematous nodules, ulcerated lesions, purpura, petechial rash, livedo reticularis	Aneurysm of hepatic artery
○ Giant cell arteritis	Erythematous nodules, ulcerated lesions, purpura	Cholestatis, nodules, biliary stenosis
Autoimmune disease		
• Lupus erythematosus	Butterfly shaped facial rash, discoid lesions, papulo-squamous lesions	Hepatitis
• Systemic sclerosis	Pruritus, hyper- or depigmentation, ulcerations, skin sclerosis, subcutaneous calcifications	Overlap with primary biliary cholangitis (Reynolds syndrome)
• Sjögren's syndrome	Raynaud's phenomenon, purpura, ichtyosis, association with other auto-immune diseases i.e., systemic lupus erythematosus, systemis sclerosis	Cholangitis, hepatitis

Given the persistence of cholestasis (alkaline phosphatases at 737 IU/L and gamma glutamine transferase at 119 IU/L), a transvenous liver biopsy was performed. Hepatic venous pressure gradient was 10 mmHg. Histology revealed a cellular infiltration of the portal tracts. The immunohistochemical analysis showed massive liver infiltration of CD117 and CD25 positive cells (Fig. 1B).

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Ductular proliferation with ductular damage, neutrophilic inflammatory infiltrate and dissecting fibrosis of the portal spaces was also present. What's your diagnosis?

Many hematological, systemic and autoimmune diseases can affect the liver and skin (Table 1). The presence of clusters of abnormal reactive and neoplastic mast cells with positive immunohistochemical staining for CD117 and CD25 in the liver is compatible with a systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) (1,2). When skin and bone marrow histology were revised (after liver histology), CD25 immunohistochemistry showed multifocal CD25 positive clusters of abnormal mast cells. Serum tryptase was elevated at 192,0 microg/L. KITD816V mutation was present. Treatment with midostaurine was started. She was non-responder and a second line therapy with avapritinib (in compassionate use) was started leading to the normalization of liver tests. The patient is still alive, after 2 years of follow up. Systemic mastocytosis is an infiltration of different organs by mast cells. Liver damage is common and can present as hepatomegaly, disturbance of liver enzymology, portal hypertension or hepatocellular insufficiency (3). Histology may show an infiltration of the portal spaces or sinusoids, cholestasis, cholangitis, nodular regenerative hyperplasia, septal and peri-sinusoidal fibrosis, veno-occlusive disease and secondary extramedullary hematopoiesis.

Keywords: cholestasis, skin lesion, systemic mastocytosis, avapritinib.

Conflict of interest statement

No conflict of interest.

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