

Paraneoplastic pemphigus associated with systemic mastocytosis

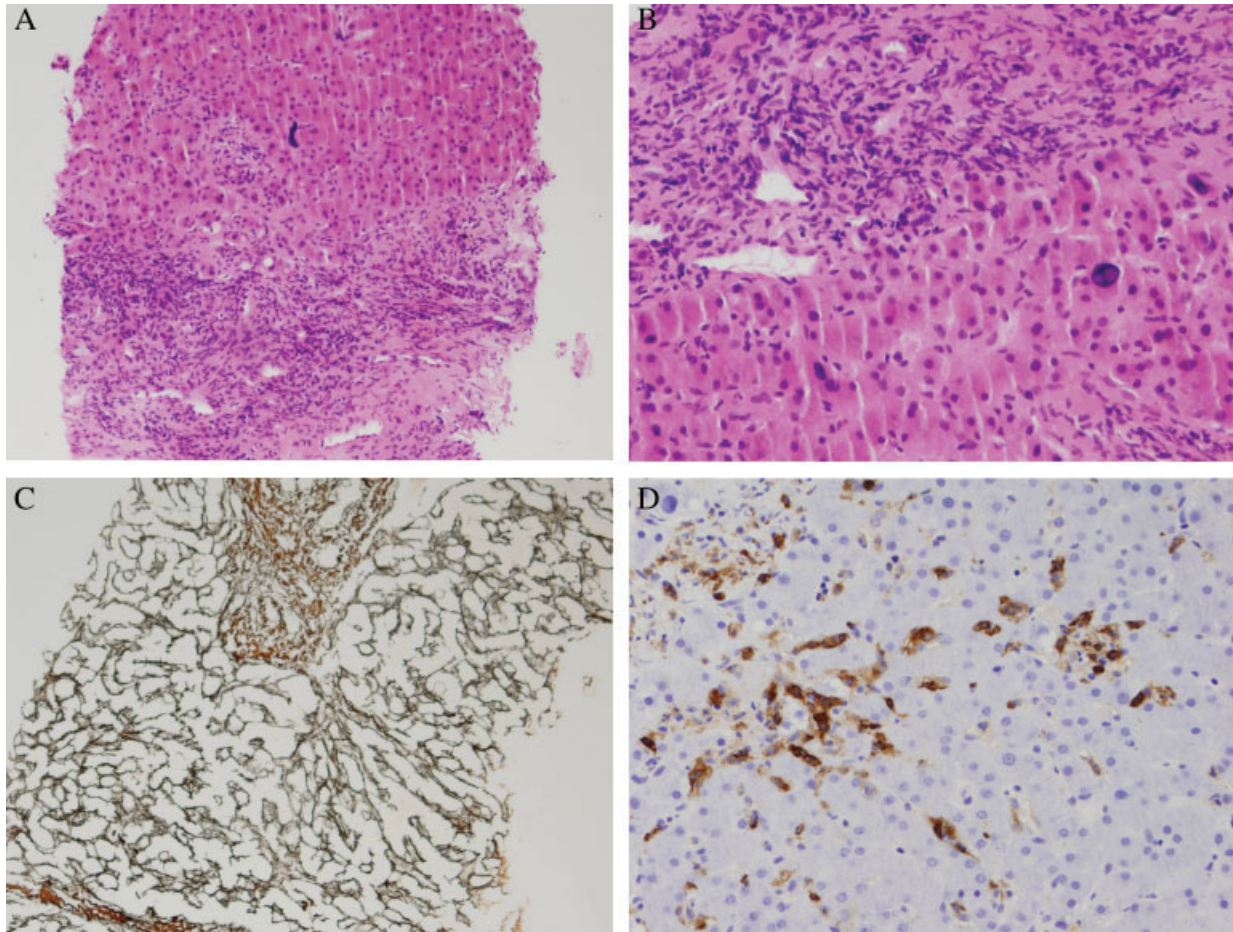
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Image 1. Liver biopsy. (A, B) Haematoxylin and eosin stain demonstrating liver architecture distorted by an infiltrate of spindle-shaped mast cells (A, $\times 100$; B, $\times 200$). (C) Silver stain demonstrating reticulin fibrosis ($\times 100$). (D) Mast cell tryptase ($\times 200$).

A 50-year-old man presented in 1996 with a pigmented papular eruption on his limbs, which urticated on rubbing. Histology confirmed the diagnosis of urticaria pigmentosa. Over the next 2 years, he developed hepatosplenomegaly and a raised serum tryptase. Attempted bone marrow aspiration yielded a dry tap, and trephine biopsy showed a hypercellular marrow with a diffuse infiltrate of mast cells with round to spindle-shaped nuclei, positive for mast cell tryptase, CD117 and CD25.

In 1998, progressive anemia led to treatment with interferon alpha, but this failed to improve his hemoglobin or symptoms. In 2000, hydroxycarbamide led to a reduction in organomegaly, at the expense of worsening anemia. He then had improvement in anemia, reduction in the size of liver and spleen, and some symptomatic improvement with 2-chlorodeoxyadenosine; he received a total of four courses over an 8-month period from 2001 to 2002. In 2006, he developed ascites in addition to increasing hepatospleno-

megaly. Liver biopsy showed a nodular architecture with widespread septal and parenchymal mast cell infiltration, again CD117 and mast cell tryptase positive (Image 1A-D), consistent with cirrhosis due to mastocytosis. Biopsy of

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Image 2. Widespread bullous and erythema multiforme-like lesions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

enlarged lymph nodes in the abdomen showed only systemic mastocytosis and no other tumor. Molecular studies identified the *c-kit* D816V mutation, which is known to be present in at least 95% of cases of systemic mastocytosis when sensitive detection methods are used. At this stage, he failed to respond to further 2-chlorodeoxyadenosine.

In December 2007, he developed severe erosive mucositis affecting the soft palate and lips, a widespread urticated and lichenoid eruption and subsequently a severe blistering rash covering over 80% of the body surface. A diagnosis of paraneoplastic pemphigus (Image 2) was confirmed by direct and indirect immunofluorescence with intercellular IgG antibodies detected on monkey esophagus to a titer of 1/400 and positive staining on rat bladder at a titer of 1/200. The rash failed to improve with high-dose prednisone (60 mg/day), high-dose intravenous immunoglobulin (2g/kg) repeated every 3 weeks for a total of four courses, and rituximab 375 mg/m². Deoxycoformycin and nilotinib were also tried over a 10-week period, in an attempt to control the underlying mastocytosis and hence the PNP, without benefit; the patient's clinical condition deteriorated and he subsequently died.

PNP is typically associated with lymphoproliferative disorders; however, to our knowledge, it has not been previously associated with systemic mastocytosis. The treatment of PNP involves treating the underlying condition, as well as the use of immunosuppressive agents, rituximab or intravenous immunoglobulin; the success of these agents is variable. Unfortunately, in this case, neither the PNP nor the underlying mastocytosis responded to multiple lines of therapy.