CASE REPORT

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Aggressive systemic mastocytosis of the liver with cholangitis

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Hepatic Oncology

Practice points

- Aggressive systemic mastocytosis may involve the liver by clusters of CD117 and tryptase-positive mast cells in portal and periportal areas as well as sinusoids and lead to liver injury.
- This article presents a case of an aggressive systemic mastocytosis with bile duct involvement mimicking primary sclerosing cholangitis.
- On the molecular level, aggressive systemic mastocytosis is defined by c-Kit point mutation D816V offering targeted therapy in tyrosine kinase inhibitors.

Mastocytosis is a clonal, neoplastic mast cell proliferation, which is in most cases restricted to the skin (cutaneous mastocytosis), but may infiltrate other organs as well (systemic mastocytosis). Involvement of the liver by a systemic mastocytosis with impairment of liver function has been recognized as sign of an aggressive course of disease (C-finding). This article presents a case of aggressive systemic mastocytosis in a 26-year-old male patient with involvement of the liver mimicking primary sclerosing cholangitis. By histology we could demonstrate multifocal clusters of atypical mast cells infiltrating portal tracts in intimate contact with bile ducts as the cause of cholangitis and liver fibrosis.

Background

In systemic mastocytosis, besides bone marrow, GI tract and spleen, the liver may become infiltrated by an accumulation of multifocal clusters of neoplastic mast cells (WHO classification of tumors of hematopoietic and lymphoid tissues); as per the definition, involvement of at least one extracutaneous organ with or without evidence of skin lesions qualifies for a systemic mastocytosis [1,2], with aggressive systemic mastocytosis being defined by additional C-findings such as impairment of liver function. Here we describe the case of a young patient suffering from aggressive systemic mastocytosis affecting bone marrow and liver leading to cholangitis and mimicking sclerosing cholangitis. In the literature, only a few cases have been described where mastocytosis infiltrates lead to liver damage with fibrosis, cirrhosis, or cholestasis due to affection of intrahepatic bile ducts [3–11].

Case

A 26-year-old man was admitted to our emergency department in reduced general condition with a stable bodyweight of 60 kg. He complained about progredient weakness, fatigue and

KEYWORDS

- liver • mastocytosis
- primary sclerosing cholangitis

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Figure 1. Conventional light microscopy of portal and partly bile duct-associated mast cell infiltrates in the liver biopsy. Arrows: mast cells with typical blue granular cytoplasmic inclusions. Magnifications: 200× (A) and 400× (B), respectively.

*Eosinophil granulocytes.

PT: Portal tract.

vomiting over the last 10 days. Furthermore, he reported paroxysmal epigastric pain over the last 6 weeks. He had no fever, diarrhea, or dyspnoe. His daily medication was pantoprazole, propranolol, mesalazin and UDCA, which was administered due to a previous diagnosis of ulcerative colitis, primary sclerosing

cholangitis and liver cirrhosis in a peripheral hospital, based on a pathologic ERCP 5 years ago. Additionally, one year ago, a diagnosis of systemic mastocytosis had been made. Except for tonsillectomy in childhood, no previous surgery was reported. Liver enzymes demonstrated cholestasis with alkaline phosphatase levels of up to 275 U/l and mildly elevated GGT levels of up to 71 U/l, whereas transaminase levels were in the normal range (Table 1). Further laboratory tests gave no indication for other underlying diseases, such as viral infection or autoimmune disease (ANA titer 1:320, but IgG near-normal). There was no evidence for drug-induced/toxic liver injury. The family history was negative for liver diseases or inflammatory bowel disease.

The patient was referred to our general ward and gastroscopy and colonoscopy showed mild gastritis and right-sided colitis with inflamed and edematous mucosa in cecum and colon ascendens. Abdominal sonography suggested the diagnosis of advanced liver fibrosis with esophageal varices. The MELD Score was 7, the Child-Pugh score was 5. During endoscopy several biopsies were collected. Routine histology of biopsies of duodenum, small bowel and colon showed multifocal, dense clusters of more than 15 large, in part spindle-shaped cells with clear cytoplasm and oval nuclei immunoreactive with antibodies against the mast cell markers CD117/c-Kit and tryptase. Other causes of colitis, that is, microscopic colitis and inflammatory bowel disease were ruled out histochemically; in addition, Langerhans cell histiocytosis was ruled out immunohistochemically with antibodies against CD207 and CD1a. By histology and immunohistology a diagnosis of systemic mastocytosis was established and the previous diagnosis of primary sclerosing cholangitis was critically questioned.

During follow-up, iliac crest biopsy was performed, showing bone marrow infiltrates of mast cells with aberrant immune phenotype with coexpression of CD25, CD117 and tryptase with c-Kit point mutation KIT D816V. The mast cell infiltrates encompassed approximately 10% of the bone marrow. The bone marrow showed intact, slightly hypocellular hematopoiesis. Morphologically there was no evidence for mast cell leukemia or an associated hematologic disease. To unravel the nature of liver injury and to further

Table 1. Serum levels during course of disease under UDCA and mesalazin treatment.

Serum parameter	06/14	07/14	10/14	11/14	04/15	7/15	Ref. val.
AP	266 [†]	275 [†]	212 [†]	214 [†]	168 [†]	229 [†]	<130 U/l
GGT	71 [†]	67 [†]	65 [†]	60 [†]	43	75 [†]	<60 U/l
Bilirubin	0.7	0.8	0.8	0.8	0.7	0.7	<1.0 mg/dl
AST	40	38	30	33	31	31	<50 U/l
ALT	35	29	26	28	28	42	<46 U/l
INR	1.15	1.09	1.15	1.10	1.06	1.02	<1.2
Tryptase						111 [†]	<11 µg/l
Hypo. erythrocyte	2.3 [†]	2.2 [†]	0.3	0.2	0.4	0.5	0–2%
Neutrophilic granulocytes	1.9 (58.6%)	3.3 (57.7%)	3.7 (64.9%)	3.2 (60.4%)	3.1 (61.2%)	2.7 (62.2%)	1.8–7.7/nl (50–80%)
Lymphocytes	1.1 (34.4%)	1.9 (33.2%)	1.6 (28.0%)	1.7 (33.0%)	1.7 (32.7%)	1.3 (30.5%)	1.0–4.8/nl (25–40%)
Monocytes	0.1 (4.5%)	0.3 (4.6%)	0.3 (4.7%)	0.2 (4.3%)	0.2 (4.0%)	0.2 (5.7%)	0.2–0.8/nl (2–9%)
Eosinophilic granulocytes	0.0 (0.6%) [†]	0.1 (2.3%)	0.1 (1.0%)	0.1 (1.1%) [†]	0.1 (1.2%) [†]	0.1 (0.8%) [†]	–0.5/nl (2–4%)
Basophilic granulocytes	0.01 (0.4%)	0.05 (0.8%)	0.05 (0.8%)	0.03 (0.5%)	0.02 (0.3%)	0.01 (0.2%)	–0.2/nl (–1%)
Thrombocytes	131 [†]	137 [†]	131 [†]	153	132 [†]	114 [†]	150–440/nl

[†]Abnormal levels.

plan therapy, a liver biopsy was obtained. The liver biopsy showed portal infiltrates of clustered atypical mast cells with clear cytoplasm and often basophilic granules (**Figure 1**). Immunohistochemically, CD117 and tryptase were demonstrated in the multifocal clusters of mast cells in portal tracts infiltrating the acinar liver parenchyma and bile ducts and vessels. By modified Gomori fiber stain a portal fibrosis with periductal preference and septal formations was detected, but no complete cirrhosis. Immunohistochemistry with antibodies against CK-7 demonstrated significant degenerative changes of the original bile ducts, ductular proliferations, and ductular metaplasia of periportal hepatocytes indicating chronic cholestasis (**Figure 2**). By histology, no signs of other specific cholangiopathies were found.

Discussion

Aggressive systemic mastocytosis is a very rare condition (>5% of all mastocytosis patients); the vast majority of systemic mastocytosis patients suffer from indolent systemic mastocytosis, whereas cutaneous mastocytosis is most frequent in children. In systemic mastocytosis, liver involvement may occur. Per definition, hepatomegaly with impairment of liver function, ascites, or portal hypertension accounts for aggressive systemic mastocytosis, whereas in indolent systemic mastocytosis only hepatomegaly without impairment of liver function may be seen (WHO classification of tumors of hematopoietic and lymphoid tissues). So far, few case reports exist describing cholestasis due to systemic mastocytosis [3–11], but only few published cases have reported a pattern suggestive typical

Figure 2. Bile duct changes due to mast cell infiltrates. Atypical mast cells infiltrating bile ducts with associated degenerative changes of the ductal epithelium and marked periductal fibrosis. Immunohistochemistry for CD117: c-Kit and cytokeratin 7. Magnification: each 400×. BD: Bile duct; CD117: c-Kit; CK7: Cytokeratin 7; H&E: Hematoxylin and eosin stain; PT: Portal tract.

for primary sclerosing cholangitis [6,12–13]. Our case represents an aggressive systemic mastocytosis with demonstrated c-Kit mutation and liver involvement mimicking primary sclerosing cholangitis. We, therefore, suggest including systemic mastocytosis in the clinical and histological differential diagnosis of chronic cholangitis besides well known entities such as primary biliary cirrhosis, primary sclerosing cholangitis, IgG4-associated cholangiopathy, and drug-induced cholestatic liver injury. Mastocytosis may be misdiagnosed [14].

There is no established curative treatment for systemic mastocytosis. Indolent cases or patients with skin involvement usually exhibit a normal life expectancy, whereas patients with aggressive systemic mastocytosis may survive only few years (WHO classification of tumors of hematopoietic and lymphoid tissues). Conservative treatment may include steroids and interferon. In our case, c-Kit point mutation D816V is known as it is present in all cases of aggressive systemic mastocytosis [15] and presents a late event during mastocytosis progression [16] and one possible option for therapy in using certain

tyrosine kinase inhibitors such as midostaurin, whereas D816V-positive mast cells appear to be resistant against imatinib [17]. Due to the young age of the patient, he is considered for allogeneic bone marrow/stem cell transplantation to offer a potential cure [2,18–19].

The patient was enrolled in the Liver Cancer Center Heidelberg.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient for the inclusion of their medical and treatment history within the case report.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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